Official Protocol Title:	A Phase 2b open-label, single-arm study to evaluate pharmacokinetics, efficacy, safety and tolerability of letermovir in pediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic haematopoietic stem cell
NCT number:	NCT03940586
Document Date:	21-Oct-2022

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 2b open-label, single-arm study to evaluate pharmacokinetics, efficacy, safety and tolerability of letermovir in pediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic haematopoietic stem cell transplantation (HSCT)

Protocol Number: 030-08

Compound Number: MK-8228

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

EudraCT	2018-001326-25
IND	104,706 (tablet) 118,361 (intravenous)

Approval Date: 21 October 2022

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 08 (global, including for Spain)	21-OCT-2022	The primary reason for Amendment 08 was Sponsor underwent entity name change and update to the address.
Amendment 07 (global including for Spain)	31-AUG-2021	The primary rationale for the changes in Amendment 07 are as follows: To provide the initial dose of oral and intravenous (IV) letermovir (LET) for Age Group 3, which has been determined by interim pharmacokinetics (PK) analyses using data from participants in Age Group 1 and Age Group 2 of this study. To add a requirement for PK sampling of hydroxypropyl-beta-cyclodextrin (HPCD), an excipient in the IV LET formulation, for Age Group 3 participants receiving the IV formulation for at least 4 consecutive days. In addition, the 10-mg oral capsule of LET is now available for use in Spain. This amendment is intended to merge Amendment 06, a country-specific amendment for Spain, with global Amendment 03, which has been used for all other participating countries, to date. Thus, Amendment 07 will be used globally, including for Spain.
Amendment 06 (country-specific for Spain)	22-NOV-2019	To add information regarding the 30-mg oral capsules of LET granules, which have now been manufactured and made available for use in Spain.

Document	Date of Issue	Overall Rationale
Amendment 05 (country-specific for Spain)	16-OCT-2019	To include all changes from Amendment 02 made in both Amendment 03 (addition of in-line filter and related requirements for administration of the IV formulation of LET and Amendment 04 (removal of the 10-mg and 30-mg oral capsules from the protocol until they become available) in the Summary of Changes table. This country-specific amendment is being released to Spain in lieu of Amendment 03, which was released to the rest of the world. Amendment 04 was not released because the Amendment 04 Summary of Changes inadvertently omitted the changes made in Amendment 03.
Amendment 04 (country-specific for Spain)	17-SEP-2019	The Spanish health authority has required that the protocol be amended to remove the 10-mg and 30-mg oral capsules from the protocol until these capsule potencies have been manufactured and the corresponding quality information has been submitted and authorized. The overall design of the protocol has not changed. Age groups requiring dosing with the 10-mg or 30-mg oral capsules will not be enrolled until a subsequent protocol amendment including these lower potency capsules has been authorized.
Amendment 03	23-AUG-2019	To add the requirement that the IV formulation of LET supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials. This requirement is being added to prevent the possible administration of product-related particulate matter. The presence of visible product-related particulate matter is an expected characteristic of new clinical supplies of the IV formulation of LET. This requirement is being implemented to allow for the release of new clinical supplies of IV LET, and, as a precaution, it must be applied regardless of whether the clinical site considers its current clinical supply to be impacted.

Document	Date of Issue	Overall Rationale
Amendment 02	15-MAR-2019	The description of the coating of the oral granule formulation to be used in this study provided in Section 2.2.4 was incorrect in the original protocol. This amendment provides the correct description of the coating of the oral granule formulation being used (Opadry coating without Surelease) and provides the rationale for selection of this oral granule formulation. Additional minor changes have been made to incorporate changes communicated in prior protocol clarification letters.
Amendment 01	24-JAN-2019	Testicular toxicity testing was removed, and creatinine clearance monitoring every 2 weeks was added to the protocol.
Original Protocol (Version 00)	08-OCT-2018	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendments:

The primary reason for Amendment 08 was Sponsor underwent entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Primary Reason for the Amendment		
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp and Dohme Corp. underwent an entity name and address change to Merck Sharp and Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Other Changes in the Amendment		
1.1 Synopsis 4.3.1 Starting Dose for This Study 6.1 Study Intervention(s) Administered	Adjusted oral and IV doses of LET to be administered in Age Group 3 participants.	To update dosing recommendations based on results of the third interim PK analysis.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities Screening/Treatment Period 4.3.1.6 Dosing in Age Group 3 5.5 Participant Replacement Strategy 8.6.1 Blood Collection for Letermovir Pharmacokinetic Sampling 9.1 Statistical Analysis Plan Summary 9.5.1 PK Analysis Population 9.6.1 Statistical Methods for Pharmacokinetic Analyses 9.7 Interim Analyses	Aligned details for the collection of intensive PK in participants on oral and IV formulations throughout the protocol.	To clarify that all Age Group 3 participants will have intensive PK, regardless of formulation used; those on oral formulation will have intensive PK on the 7th consecutive day of oral LET while those on IV formulation will have intensive PK on the 5th consecutive day of LET administration.
2.2.5 Ongoing Clinical Studies	Deleted text of ongoing studies and added statement to refer to the Investigator's Brochure (IB).	To align with the most current version of the IB.
4.4 Beginning and End of Study Definition	Included a reference to Section 7.3 instead of a definition that is provided in Section 7.3.	To clarify definition of lost to follow-up by referring to the appropriate section.

Section # and Name	Description of Change	Brief Rationale
4.4.1 Clinical Criteria for Early Study Termination	Revised language about early termination based on changing benefit/risk ratio.	To correct grammar and ensure clarity and intent of the section.
5 Study Population	Added statement about the collection of demographic data and participant confidentiality.	To clarify the collection, use, and confidentiality of demographic data provided by the participants to align with the EU CTR.
6.1 Study Intervention(s) Administered	Added a cross-reference to Appendix 7.	To align with recent PMDA regulation changes.
6.1 Study Intervention Table	Revised column heading and footnotes to include AxMP. Changed 'Experimental' in the 'Use' column to 'Test Product.	To align with EU CTR.
7.3 Lost to follow-up	Deleted note describing loss to follow-up.	To allow individual studies to select language related to "lost to follow-up" that is appropriate for the study.
8.1.9 Study Intervention Administration	Added parenthetical to allow a qualified designee to prepare IV study intervention.	To clarify who is responsible for preparing IV study intervention.
8.4.7 Events of Clinical Interest (ECIs)	Revised language defining potential DILI.	To clarify for the investigator/site to define what a potential DILI is and to align with this acronym being used in the reporting table.

Section # and Name	Description of Change	Brief Rationale
8.6.2.1 Additional Creatinine Clearance Measurements for Participants in Age Group 3 Receiving Intravenous Letermovir Formulation	Consolidated rows in Table 15.	To clarify when samples for creatinine clearance in participants receiving IV LET should be collected.
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events 10.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added details on the definition and recording of medication error, misuse, and abuse.	To align with EU CTR.
Throughout	Minor administrative formatting, grammatical, and typographical changes were made throughout the document.	The ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b open-label, single-arm study to evaluate pharmacokinetics, efficacy, safety and tolerability of letermovir in pediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic haematopoietic stem cell transplantation (HSCT)

Short Title: LET for the prevention of CMV infection/disease in pediatric HSCT recipients

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There are no hypotheses to be tested in this study.

In pediatric (birth to <18 years of age) participants who received an allogeneic HSCT and are at risk for CMV infection and/or disease:

Objectives	Endpoints
Primary	
Objective: To evaluate letermovir PK in pediatric participants grouped by age.	AUC0-24, Cmax (for participants receiving oral formulation), Ceoi (for participants receiving IV formulation), and Ctrough
Secondary	
To evaluate the safety and tolerability of treatment with letermovir through Week 48 post-transplant based on the proportion of participants with adverse events.	Adverse Events (AEs) AEs Resulting in Study Medication Discontinuation
To evaluate the efficacy of letermovir in prevention of clinically significant CMV infection through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant.	Clinically significant CMV infection (CS-CMVi, defined as initiation of preemptive therapy [PET] for documented CMV viremia and/or CMV disease).
To evaluate the palatability and acceptability of treatment with letermovir oral granules.	Score on a palatability scale.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Prevention
Indication	Prevention of clinically significant CMV infection in pediatric allogeneic HSCT recipients
Population	Pediatric participants receiving HSCT at risk for CMV infection and/or disease
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 44 months from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact.

Number of Participants:

Approximately 60 participants will be allocated/enrolled.

Intervention Groups and Duration:

Intervention Groups

The study will enroll participants in 3 Age Groups:

- Age Group 1: From 12 to <18 years of age (adolescents)
- Age Group 2: From 2 to <12 years of age (children)
- Age Group 3: From birth to <2 years of age (neonates, infants and toddlers)

All participants will receive open-label LET for 14 weeks (~100 days) post-transplant. The following tables show estimated starting oral and intravenous (IV) doses of LET for participants in Age Groups 1 (12 to <18 years) and 2 (2 to <12 years). The starting doses are based on available PK data from adult HSCT recipients and will be confirmed or modified based upon a review of interim PK, safety and tolerability results in the dose-finding panels of Age Groups 1 and 2 (Panel A). Doses for Age Group 3 (birth to <2 years) are based on the accumulated PK, safety, and tolerability data from Age Group 1 (Panels A and B) and Age Group 2 Panel A.

Oral Letermovir Dosing Table

Age Group	Age Range	BW limits (kg)	Oral dose LET (mg)	Oral dose LET (mg) with CsA
1	12 to <18 years	Any weight	480	240
2	2 to <12 years	≥30	480	240
		18 to <30	240	120
		10 to <18	120	60
3	birth to <2 years	10 to ≤15	120	60
		7.5 to <10	120	60
		5.0 to <7.5	60	40
		2.5 to <5.0	40	20

BW=body weight; CsA=Cyclosporin A; LET=letermovir; PK=pharmacokinetics.

Intravenous Letermovir Dosing Table

Age Group	Age Range	BW limits (kg)	IV dose LET (mg)	IV dose LET (mg) with CsA
1	12 to <18 years	Any weight	480	240
2	2 to <12 years	≥30	240[a]	240[b]
		18 to <30	120[a]	120[b]
		10 to <18	60[a]	60[b]
3	birth to <2 years	10 to ≤15	60[a]	60[b]
		7.5 to <10	60[c]	60[b,c]
		5.0 to <7.5	40[c]	40[b,c]
		2.5 to <5.0	20[c]	20[b,c]

BW=body weight; CsA=Cyclosporin A; IV=intravenous; LET=letermovir; PK=pharmacokinetics.

[a] Based on modeling, for Age Group 2 and Age Group 3, the IV dose of LET without CsA is reduced by 50% compared with oral LET in order to maintain target exposures.

[b] No further reduction of IV LET is necessary when coadministered with CsA.

[c] Based on interim analyses results, doses are increased for participants weighing <10 kg in Group 3.

Total Number	1 (single-arm study)
Duration of Participation	Each participant will participate in the study for approximately 50 weeks from the time the participant or the participant's legal representative provides documented informed consent/assent through the final contact. Participants can be screened from up to 15 days prior to receipt of HSCT to 28 days post-HSCT. Enrollment/allocation can be initiated as early as the day of transplant, but must be completed by Day 28 post-transplant. All participants will receive treatment until Week 14 post-transplant. After the end of treatment, each participant will be followed until Week 48 post-transplant.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1.	

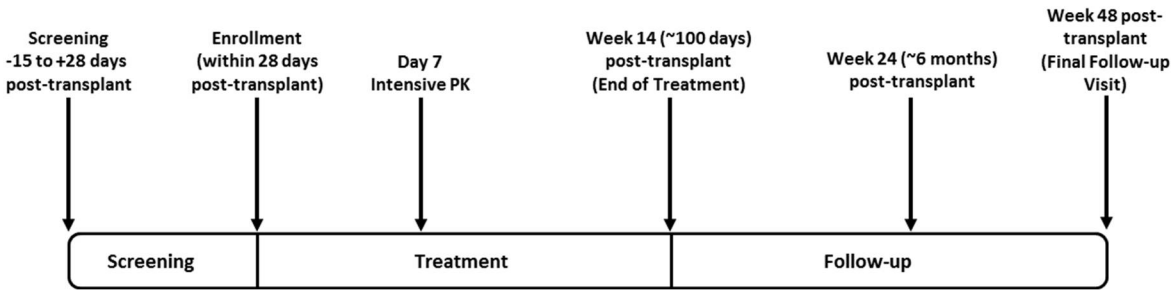
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 13.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



PK=pharmacokinetics.

Refer to Figure 2 (Section 4.1) for further details of study design (sequential enrollment).

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities Screening/Treatment Period

Study Period		Treatment Period[a]														End of Treatment Visit	CMV Infection Visit[b]	Early Study Discon Visit[c]	Notes **(Protocol Section Reference for further details)**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	25	26	
Visit Name	SCR[d]	D1[d]	D7	W2	W3	W4	W5	W6	W7	W8	W9	W 10[e]	W 11[e]	W 12[e]	W 13[e]	W14[e]			**Days and Weeks correspond to the time since enrollment (Day 1)[e]**
Visit Window			+2 days	+/-3 days															
Administrative Procedures																			
Informed Consent/Assent	X																		
Informed Consent for FBR (optional)	X																		
Participant Identification Card	X																		
Inclusion/Exclusion Criteria	X	X																	
Medical History	X																		
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Varies by study period (Section 8.1.5)
Treatment Allocation		X																	
Study intervention dispensing		X		X		X		X		X		X		X					Contact IRT at all dispensing visits (Section 8.11.2.2).

Study Period		Treatment Period[a]														End of Treatment Visit	CMV Infection Visit[b]	Early Study Discon Visit[c]	Notes **(Protocol Section Reference for further details)**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	25	26	
Visit Name	SCR[d]	D1[d]	D7	W2	W3	W4	W5	W6	W7	W8	W9	W 10[e]	W 11[e]	W 12[e]	W 13[e]	W14[e]			**Days and Weeks correspond to the time since enrollment (Day 1)[e]**
Visit Window			+2 days	+/-3 days															
Study intervention administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Participants discharged on oral granules to be taken in the outpatient setting must be trained on correct procedure for preparing and administering the formulation (Section 8.11.2.2).
HSCT Details Review		X																	
Study Medication Diary Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Participant/caregiver will be trained in the use of the paper study medication diary prior to discharge from hospital (Section 8.1.9.2).
Safety Procedures																			
Full Physical Examination	X	X																	
Height	X	X		X		X		X		X		X		X		X	X	X	
Weight	X	X		X		X		X		X		X		X		X	X	X	Weight recorded at enrollment (Day 1) will be used to determine initial dosing. Thereafter, the dose must be adjusted according to the most recent body weight (Section 8.3.1).
Targeted Physical Examination			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Performed only when clinically indicated (Section 8.11.2).
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period		Treatment Period[a]														End of Treatment Visit	CMV Infection Visit[b]	Early Study Discon Visit[c]	Notes **(Protocol Section Reference for further details)**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	25	26	
Visit Name	SCR[d]	D1[d]	D7	W2	W3	W4	W5	W6	W7	W8	W9	W 10[e]	W 11[e]	W 12[e]	W 13[e]	W14[e]			**Days and Weeks correspond to the time since enrollment (Day 1)[e]**
Visit Window			+2 days	+/-3 days															
12-Lead Electrocardiogram (ECG)	X															X	X	X	Performed locally; ECG only required at CMV infection visit or the Early Study Discontinuation visit if the participant was on study therapy at the time of the visit (Section 8.3.3).
Child-Pugh Score	X	X		X		X		X		X		X		X		X	X	X	
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Varies by study period (Section 8.4)
Hematology	X	X		X		X		X		X		X		X		X	X	X	Performed locally. Section 8.3.4 & Appendix 2. Creatinine clearance and liver function tests must also be evaluated in all participants within 5 days prior to enrollment.
Chemistry	X	X		X		X		X		X		X		X		X	X	X	
Creatinine Clearance	X	X		X		X		X		X		X		X		X	X	X	Calculated per equations provided in Appendix 12. See Section 7.1 for criteria for discontinuation from study intervention. See Section 8.6.2.1 for additional monitoring requirements for Age Group 3 participants on IV LET.
Coagulation PT/INR	X	X		X		X		X		X		X		X		X	X	X	Performed locally (Appendix 2)
Urinalysis	X	X														X	X	X	Performed locally

Study Period		Treatment Period[a]														End of Treatment Visit	CMV Infection Visit[b]	Early Study Discon Visit[c]	Notes **(Protocol Section Reference for further details)**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	25	26	
Visit Name	SCR[d]	D1[d]	D7	W2	W3	W4	W5	W6	W7	W8	W9	W 10[e]	W 11[e]	W 12[e]	W 13[e]	W14[e]			**Days and Weeks correspond to the time since enrollment (Day 1)[e]**
Visit Window			+2 days	+/-3 days															
Date of menarche (females only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Review at each visit as appropriate in prepubescent female participants. Once a date of menarche has been confirmed, participant is considered to be a WOCBP.
Pregnancy Test (urine or serum tests for WOCBP only)	X	X				X				X						X	X	X	Performed locally (Appendices 2 and 5)
Participant Confirmation of Birth Control (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
HIV and Hepatitis B and C Screen	X																		Performed locally (Appendix 2)
Patient Reported Outcome																			
Palatability and Acceptability Assessment (pediatric oral granules only)		←----------X----------→																	Palatability assessment should occur on the first day of oral granule administration by mouth and be repeated 1 week later. **Not required for participants receiving oral granules via G tube/NG tube** (Section 8.10).

Study Period		Treatment Period[a]														End of Treatment Visit	CMV Infection Visit[b]	Early Study Discon Visit[c]	Notes **(Protocol Section Reference for further details)**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	25	26	
Visit Name	SCR[d]	D1[d]	D7	W2	W3	W4	W5	W6	W7	W8	W9	W 10[e]	W 11[e]	W 12[e]	W 13[e]	W14[e]			**Days and Weeks correspond to the time since enrollment (Day 1)[e]**
Visit Window			+2 days	+/-3 days															
CMV Procedures/Assessments																			
CMV DNA PCR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Performed locally (Section 8.2.1) CMV DNA PCR must also be performed within 5 days prior to enrollment in all participants.
CMV Disease Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CMV DNA Sequence Analysis																	X		**Plasma** sample required (Section 8.2.2)
PET Initiation/ Treatment of CMV Disease																	X		CMV DNA PCR must be collected on the same day as PET initiation/treatment of CMV disease.
PK/Biomarkers																			
Buccal Swab for Planned Genetic Analysis	X																		Buccal swab should be obtained *prior to transplant* when possible (Sections 8.8 and 8.9).
Sparse PK				X		X		X		X		X		X		X	X	X	Collected within 2 hours predose for all study **participants on study intervention** (Section 8.6.1)
Intensive PK on oral formulation at Day 7 visit (Panel A)			X																All participants in Panel A of Age Groups 1 and 2 who receive oral formulation of LET from D1 until D7 visit will have intensive PK. Section 8.6.1 for PK time points.

Study Period		Treatment Period [a]														End of Treat-ment Visit	CMV Infection Visit[b]	Early Study Discon Visit[c]	Notes **(Protocol Section Reference for further details)**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	25	26	
Visit Name	SCR[d]	D1[d]	D7	W2	W3	W4	W5	W6	W7	W8	W9	W 10[e]	W 11[e]	W 12[e]	W 13[e]	W14[e]			**Days and Weeks correspond to the time since enrollment (Day 1)[e]**
Visit Window			+2 days	+/-3 days															
Intensive PK on oral formulation (Age Group 3)			←----------X----------→																All participants in Age Group 3 will have intensive PK sampling done (starting on the 7th consecutive day of oral LET, **only in participants who did not previously have intensive PK on IV formulation**) (Section 8.6.1).
Intensive PK on IV formulation			←----------X----------→																Start on the 5th consecutive day of IV dosing and **only in participants who did not previously have intensive PK** on oral formulation (Section 8.6.1).
HPCD PK sampling (for Age Group 3 participants on IV formulation only)			←----------X----------→																Start on the 4th consecutive day of IV dosing. See Sections 8.6.2 & 8.6.2.1 for timepoints and additional requirements for creatinine clearance monitoring.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = β-Human Chorionic Gonadotropin; CMV = cytomegalovirus; CS-CMVi = clinically significant CMV infection; Discon = discontinuation; DNA = deoxyribonucleic acid; D = day; EOT = end of treatment; FBR = Future Biomedical Research; FSH = follicle- stimulating hormone; FU = follow-up; HPCD = hydroxypropyl-beta-cyclodextrin; HIV = human immunodeficiency virus; h = hour; HSCT = hematopoietic stem cell transplant; IRT = interactive response technology; IV = intravenous; LET = letermovir; LH = luteinizing hormone; PCR = polymerase chain reaction; PET = preemptive therapy; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; SCR = screening; W = week; WOCBP = woman of childbearing potential.

[a] The "treatment period" is defined as the period from Day 1 through Week 14 post-transplant, regardless of when a participant stops taking LET. Day 1 will be the day of enrollment when LET will be initiated. Study intervention may begin as early as the day of transplant and no later than 28 days post-transplant. Study intervention will continue through Week 14 (~100 days) post-transplant. Day 1 procedures/assessments must be performed prior to first dose of study intervention.

[b] The visit will be a CMV Infection Visit for all participants who meet the endpoint of CS-CMVi defined as the occurrence of CMV disease or the initiation of PET. During the treatment period, LET must be discontinued (if the participant is still on LET). All procedures indicated in the SoA should be completed prior to initiating PET for CMV infection or treatment for CMV disease at this visit.

[c] The visit will be an Early Study Discontinuation Visit for those participants who are prematurely discontinued from the study (not study intervention alone) through Week 24 post-transplant. All procedures indicated in the SoA should be performed at this visit prior to discontinuing the participant from the study.

[d] Participants may be screened during a period starting from 15 days prior to transplantation until no later than 28 days post-transplant. Participants will have CMV viremia assessed using a CMV DNA PCR assay. After establishing absence of CMV viremia, participants should be tested once a week until enrollment (Day 1). The following are to be assessed within 5 days prior to enrollment: CMV DNA, Child-Pugh Score; serum AST, ALT, and total bilirubin; and creatinine clearance. Note: Screening and enrollment (Day 1) Visits will occur on separate days.

[e] All participants will receive treatment ***until Week 14 post-transplant***. The EOT Visit will coincide with Week 10, Week 11, Week 12, Week 13 or Week 14 depending on the day the participant was enrolled relative to the day of transplant as follows:

For participants enrolled from the day of transplant to 6 days post-transplant, participants attend Day 1 to Week 13 (Visits 1-15) and Week 14 (Visit 16) will be the EOT Visit.

For participants enrolled from Day 7 to Day 13 post-transplant, participants attend Day 1 to Week 12 (Visits 1-14) and Week 13 (Visit 15) will be the EOT Visit.

For participants enrolled from Day 14 to Day 20 post-transplant, participants attend Day 1 to Week 11 (Visits 1-13) and Week 12 (Visit 14) will be the EOT Visit.

For participants enrolled from Day 21 to Day 27 post-transplant, participants attend Day 1 to Week 10 (Visit 1-12) and Week 11 (Visit 13) will be the EOT Visit.

For participants enrolled on Day 28 post-transplant, participants attend Day 1 to Week 9 (Visits 1-11) and Week 10 (Visit 12) will be the EOT Visit.

All procedures listed under Visit No. 16, EOT Visit, should be performed at the true end of treatment.

After the EOT Visit, all study participants should enter follow-up (Visit No. 17). Refer to SoA Follow-up Period Section 1.3.2.

1.3.2 Schedule of Activities Follow-up Period

Study Period	Follow-up Period (through Week 24 post-transplant)					Follow-up Period (through Week 48 post-transplant)			CMV Infection Visit[a]	Early Study Discon Visit (follow-up)[b]	Notes (Protocol Reference Section for further details)
Visit Number	17	18	19	20	21	22	23	24	25	26	
Visit Name	W16	W18	W20	W22	W24	W32	W40	W48			Weeks correspond to **weeks post-transplant.**
Visit Window	+/-4 Days										
Administrative Procedures											
Contact						X	X	X			Virtual Visit, not a site visit
Concomitant Medication Review	X	X	X	X	X	X	X	X	X		Varies by study period (Section 8.1.5)
Safety Procedures											
Height		X							X	X	
Weight		X							X	X	
Targeted Physical Examination	X	X	X	X	X				X	X	Performed only when clinically indicated (Section 8.3.1)
Vital Signs	X	X	X	X	X				X	X	Heart rate, blood pressure, respiratory rate, and body temperature (Section 8.3.2)
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	Varies by study period (Section 8.4)
Hematology		X							X	X	Performed locally (Section 8.3.4)
Chemistry		X							X	X	Performed locally (Section 8.3.4)
Creatinine Clearance		X							X	X	Calculated per equations provided in Appendix 12. See Section 7.1 for discontinuation criteria for study intervention.
Urinalysis		X							X	X	Performed locally (Section 8.3.4)

Study Period	Follow-up Period (through Week 24 post-transplant)					Follow-up Period (through Week 48 post-transplant)			CMV Infection Visit[a]	Early Study Discon Visit (follow-up)[b]	Notes (Protocol Reference Section for further details)
Visit Number	17	18	19	20	21	22	23	24	25	26	
Visit Name	W16	W18	W20	W22	W24	W32	W40	W48			Weeks correspond to **weeks post-transplant.**
Visit Window	+/-4 Days										
Date of menarche (females only)	X	X									Review at specified visits as appropriate in prepubescent female participants. Once a date of menarche has been confirmed, participant is considered to be a WOCBP.
Pregnancy Test (urine or serum for WOCBP only)	X	X									Performed locally (Appendices 2 and 5)
Participant Confirmation of Birth Control (WOCBP only)	X	X									Acceptable methods of contraception to be used from the time of consent/assent through 28 days after the last dose of study intervention (Appendix 5).
CMV Procedures/Assessments											
CMV DNA PCR	X	X	X	X	X				X	X	Performed locally (Section 8.2.1)
CMV Disease Assessment	X	X	X	X	X				X	X	
CMV DNA Sequence Analysis									X		**Plasma** sample required. Performed only in participants with CS-CMVi
PET Initiation/Treatment of CMV Disease									X		

AE = adverse event; CMV = cytomegalovirus; CS-CMVi = clinically significant CMV infection; Discon = discontinuation; DNA = deoxyribonucleic acid; FU = follow-up; LET = letermovir; PCR = polymerase chain reaction; PET = preemptive therapy; W = week; WOCBP = women of childbearing potential.

[a] The visit will be a CMV Infection Visit for all participants who meet the endpoint of CS-CMVi (defined as the occurrence of CMV disease or the initiation of PET) through Week 24 post-transplant. During the treatment period, LET must be discontinued (if the participant is still on LET). All procedures indicated in the SoA should be completed ***prior to*** initiating PET for CMV infection or treatment for CMV disease at this visit.

[b] The visit will be an Early Study Discontinuation Visit for those participants who are prematurely discontinued from the study through Week 24 post-transplant. All procedures indicated in the SoA should be performed at this visit prior to discontinuing the participant from the study.

2 INTRODUCTION

Letermovir (LET, also known as MK-8228, AIC246, AIC001) is an inhibitor of the CMV viral terminase inhibitor and has been approved for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients (R+) of an allogeneic HSCT.

2.1 Study Rationale

In a pivotal, global, Phase 3 study (P001), LET was demonstrated to be effective in the prevention of CMV infection and disease in adult R+ allogeneic HSCT recipients. LET has been developed and approved for adult CMV-seropositive allogeneic HSCT recipients (R+). The purpose of this study is to assess PK, safety, tolerability, and efficacy of LET in pediatric allogeneic HSCT recipients aged birth to <18 years.

The pathogenesis and manifestations of CMV disease are similar in adults and in pediatric patients [Castagnola, E., et al 2004]. Therefore, LET is anticipated to have a similar safety and efficacy profile in pediatric patients when given at doses that achieve a similar exposure to that observed in adult patients. The PK data obtained in this study will be used to update currently available population PK and physiologically based pharmacokinetics (PBPK) models based on adult PK data to support dosing recommendations in the pediatric population.

2.2 Background

Refer to the IB for detailed background information on LET.

2.2.1 Pharmaceutical and Therapeutic Background

LET is a novel inhibitor of the CMV viral enzyme DNA terminase, which cleaves newly synthesized CMV DNA into individual viral genomes and guides them into empty viral capsids. The mechanism of action of LET is highly specific, suggesting a limited potential for mechanism-based toxicity.

LET is currently available as an oral formulation (tablets) and an intravenous (IV) formulation for use in adult allogeneic HSCT recipients. Participants in this study will either receive the currently marketed oral adult tablets (240-mg strength or multiples thereof) or the newly developed age-appropriate pediatric oral formulation (consisting of encapsulated coated granules of LET; henceforth referred to as “oral granules”) for oral administration (see Section 2.2.4 for the bioavailability evaluation of the oral granules). During the course of the study, participants may use the IV formulation when a transient condition (such as vomiting) precludes oral intake. The IV formulation that will be used in P030 will be the same IV formulation previously used in adult participants in P001 and currently marketed for adult administration.

2.2.2 Cytomegalovirus in HSCT Recipients

CMV infection is common. It is generally acquired early in life, with the majority of the adult population being CMV-seropositive in most countries. Similar to other herpes viruses, acute infection is generally followed by latent (dormant) infection. Among individuals with intact immune systems, reactivation of CMV infection is uncommon and generally asymptomatic. However, CMV reactivation in immunocompromised patients, such as transplant recipients, can cause significant morbidity and mortality.

Data on the number of HSCTs by age group in pediatric patients are limited. Preliminary data on allogeneic HSCTs (unpublished) from 358 centers in Europe across 46 countries for the years 2008 to 2012 provided by the European Group for Blood and Marrow Transplantation (EBMT) are summarized in Table 1. During this period 62,940 HSCT transplants took place, of which 13,513 (21.4%) were performed in children up to 18 years of age.

Table 1 Number of Haematopoietic Stem Cell Transplantation by Age Group

Age Group[a]	**Number (%)**
0-23 months	2,280 (3.6% of 62940)
2-11 years	7,277 (11.5% of 62940)
12- <18 years	3,956 (6.2% of 62940)
All children (0- <18 years)	13,513 (21.4% of 62940)
≥18 years	49,427 (78.6% of 62940)
[a] EBMT Data from 358 centers in 46 countries in the EU, 2008-2012	

Table 2 shows the distribution of allogeneic HSCTs in the US by age group in 2014 [Center for International Blood and Marrow Transplant Research 2017]. As seen in the European database, approximately 20% of HSCTs performed in United Stated were performed in the pediatric subpopulation.

Table 2 Distribution of Allogeneic Haematopoietic Stem Cell Transplantations in 2014 in the United States

Age at Transplant (Years)	**Number (%)**
0-10	908 (10.7%)
11-20	703 (8.3%)
21+	6,859 (81.0%)
Total	8,470 (100%)

[Center for International Blood and Marrow Transplant Research 2017]

CMV seropositivity in either transplant recipients or donors is associated with increased mortality post-transplant [Emery V, Zuckerman M, Jackson G, Aitken C, Osman H 2013] [Tomonari, A., et al 2007]. In HSCT recipients, the risk of CMV reactivation and progression to disease is greatest in CMV-seropositive recipients, where up to 80% of recipients are likely to reactivate CMV, regardless of the serostatus of the donor (D-/R+ or D+/R+) [Ljungman, P., et al 2011] [Ljungman, P. 2014] [Razonable, R. R. 2005] [Zhou, W., et al 2009]. The highest risk period for developing CMV infection (as defined by detectable CMV DNA) is during the first 100 days post-transplant [Özdemir, E., et al 2007].

Worldwide, CMV seroprevalence increases with increasing age (Table 3). In the US, seroprevalence is between 5% to 20% in children between 0 to 5 years of age [Cannon, M. J., et al 2010] and increases to around 42.7% for children 12 to 19 years of age [Bate, S. L., et al 2010]. A similar trend in increasing CMV seroprevalence with increasing age was also reported in studies from the European Union (EU) [Just-Nubling, G., et al 2003] [Ludwig, A. 2009] [Lopo, S., et al 2011].

Table 3 Cytomegalovirus Seroprevalence in General Population, United States

Age Group	**Seroprevalence (%)**
0-5 years[a]	5-20
6-11 years[b]	34-41
12-19 years[b]	40-46
20-29 years[b]	46-53
30-39 years[b]	53-60
40-49 years[b]	55-61
>50 years[a]	65-90
[a] Cannon, 2010 [b] Bate, 2010	

[Cannon, M. J., et al 2010] [Bate, S. L., et al 2010]

Given the relatively small number of HSCTs performed in pediatric patients and the lower CMV seroprevalence in younger individuals, enrollment in the current study may be challenging, particularly in the youngest age group. These considerations have been taken into account when designing the study to enable broad enrollment across the subpopulation of HSCT recipients.

The clinical effects of CMV infection can be divided into direct and indirect effects [Ljungman, P., et al 2002] [Boeckh, M. 2011]. The direct effects include the spectrum of CMV disease manifestations, including pneumonia, hepatitis, retinitis, and encephalitis; these are associated with considerable morbidity and mortality [Boeckh, M. and Geballe, A. P. 2011] [Ljungman, P., et al 2002] [Boeckh, M. 2011].

The indirect effects of CMV infection include increased risk of opportunistic bacterial and invasive fungal infections, graft-versus-host disease (GVHD), and nonrelapse mortality

[Craddock, C., et al 2001] [Miller, W., et al 1986] [Özdemir, E., et al 2007] [Martino, R., et al 2001] [Söderberg, C., et al 1993] [Larsson, K., et al 2004] [Marty, F. M. and Boeckh, M. 2011] [Ariza-Heredia, E. J., et al 2014]. Since the introduction of PET for the management of CMV reactivation in allogeneic HSCT recipients, the incidence of CMV disease has been dramatically reduced. However, allogeneic HSCT patients have a high likelihood of developing CMV viremia [Ariza-Heredia, E. J., et al 2014], which is associated with an increased risk of overall mortality [Green, M. L., et al 2016].

CMV Prevention in HSCT recipients

There are 2 approaches to preventing CMV disease in HSCT recipients: 1) prophylaxis with antivirals, and 2) PET, defined as the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV viremia is detected [Ljungman, P., et al 2002].

With the exception of LET, all other available anti-CMV agents are nucleoside analogues with associated toxicities including myelosuppression and nephrotoxicity that limit their clinical utility in the HSCT setting.

Due to the concerns for toxicities associated with the nucleoside analogue anti-CMV agents, PET is generally preferred to prophylaxis, and has been the preferred approach for preventing CMV disease in the majority of HSCT transplant centers worldwide, especially during the first 100 days post-transplant. However, PET is suboptimal for several reasons:

- PET is initiated after patients develop CMV viremia. A recent study concluded that CMV viremia is associated with an increased risk of overall mortality regardless of the initiation of PET [Green, M. L., et al 2016].

- Given the toxicities associated with anti-CMV agents, it is important not to initiate PET unless it is clear that the benefit outweighs the risks. However, there is no universally accepted viral load threshold for the initiation of PET to guide clinicians when to initiate PET [Romkens, T. E., et al 2016].

Based on these considerations, a safe and efficacious prophylaxis strategy offers advantages over PET. LET, an anti-CMV agent with a novel mechanism of action, has recently been shown to be generally well tolerated and efficacious in a pivotal Phase 3 study (P001) when used for CMV prophylaxis in adult CMV-seropositive HSCT recipients (refer to accompanying the IB for further details). It has recently been approved and is available in several regions of the world for CMV prophylaxis in adult HSCT recipients. CMV prophylaxis with LET will likely represent a paradigm shift from the practice of PET with nucleoside analogues for CMV prevention currently employed by most transplant centers worldwide. The current study will evaluate the PK, safety, and efficacy of LET in this subpopulation of HSCT recipients.

2.2.3 Pharmacokinetic Background of LET

In the clinical development program for LET, population pharmacokinetics, exposure-response models and PBPK modeling supported the characterization of LET pharmacokinetics in healthy adult participants and HSCT recipients.

2.2.3.1 LET, Absorption, Metabolism, and Disposition

Based on population PK analyses, LET bioavailability in HSCT patients is approximately 35%, while coadministration with CsA increases bioavailability to approximately 85% (Table 4). The population mean total volume of distribution is estimated to be 45.5 L in HSCT recipients. LET is extensively bound (98.7%) to human plasma protein in vitro and there was no dependence on concentration over the range from 0.2 to 50 mg/L. Biliary excretion is the major route of elimination and LET is primarily eliminated as parent drug (~70% of dose) and an acyl-glucuronide (~6% of dose) in human feces. In vitro studies indicated that LET is a substrate of UGT1A1 and UGT1A3 and the hepatic uptake transporters OATP1B1 and OATP1B3. Drug interaction studies with the OATP1B inhibitor CsA increased LET exposure suggesting that OATP1B plays a central role in the elimination of LET. Although LET is a substrate of CYP3A, CYP2D6, and CYP2J2 in vitro, oxidative metabolism of LET is a minor pathway in vivo.

2.2.3.2 Drug Interactions Between LET and Immunosuppressant Agents

The Effect of Immunosuppressant Agents on LET:

CsA is an inhibitor of CYP3A, P-gp, OATP1B1/3, and several other transporters. In Phase 1 drug-drug interaction (DDI) studies, coadministration of LET with 50- or 200-mg CsA resulted in approximately 1.9- to 3.4-fold increase in AUC and 1.5- to 2.7-fold increase in Cmax of LET. These results in the presence of CsA are consistent with the Phase 3 population PK analyses in adult HSCT recipients (Table 1). Therefore, the adult LET dose of 480 mg is reduced to 240 mg QD when coadministered with CsA. Tacrolimus and mycophenolate mofetil do not affect LET plasma concentrations and sirolimus is not anticipated to affect LET plasma concentrations.

The Effect of LET on Immunosuppressant Agents:

Coadministration of 240-mg QD oral LET with a single dose of 50-mg CsA resulted in 66% and 8% increase in CsA AUC and Cmax, respectively. Coadministration of 480-mg QD oral LET with a single dose of 5-mg tacrolimus resulted in 2.42- and 1.57-fold increase in tacrolimus AUC and Cmax, respectively. In the case of sirolimus, 3.40- and 2.76-fold increases in sirolimus AUC and Cmax, respectively, were observed following coadministration of 480-mg QD oral LET with 2-mg sirolimus. However, there was no clinically relevant effect of LET on mycophenolate mofetil. Coadministration of LET increases the exposures of the immunosuppressants (CsA, sirolimus, and tacrolimus). Frequent monitoring of CsA, sirolimus, or tacrolimus whole blood concentrations should be performed during and at discontinuation of LET and the dose of immunosuppressant should

be adjusted accordingly. The dose of LET is not adjusted when LET is given with tacrolimus, sirolimus, or mycophenolate mofetil.

For the full description of other DDI studies with LET, refer to the IB or the local prescribing information (if available) for LET.

2.2.3.3 Pharmacokinetic Modeling and Simulation in Adults

There are currently no PK data for LET in pediatric patients. In order to guide dose selection for the proposed clinical study in pediatric participants, the Phase 3 population PK model, as well as a PBPK model based on adult data, will be used.

A Phase 1 population PK model was developed to characterize the nonlinear and time-varying LET PK in healthy adult participants, and to evaluate the effects of selected intrinsic factors [Prohn M, Dykstra K, Cho C, et al. 2017]. The final PK model is a 4-compartment open model with first-order elimination and nonlinearity on clearance (CL) and intercompartmental clearance (Q1). The Phase 1 population PK model identified a statistically significant increase in both the maximum CL and volume of distribution (Vd) with an increase in body weight, and a race effect (Asian) on Vd.

A Phase 3 population PK model was developed using data pooled from the Phase 3 study (P001), one Phase 2b study, and 3 Phase 1 studies, to characterize LET steady-state PK in adult HSCT recipients at the clinical dose, and to evaluate the effects of selected intrinsic and extrinsic factors on the PK of LET [Viberg A, Prohn M, Dykstra K, et al. 2017]. The final PK model is two-compartment with linear absorption and clearance (dose proportional). The only significant covariates identified were a race effect (Asian) that decreased peripheral volume, and CsA coadministration that increased bioavailability and decreased clearance. Overall, oral bioavailability of LET was approximately 35%, increasing to approximately 85% with CsA coadministration. LET clearance was 4.84 L/h, decreasing to 3.38 L/h with CsA coadministration.

The Phase 3 population PK model was used to estimate LET exposures in HSCT recipients given LET 480 mg QD oral or IV, or 240 mg when coadministered with CsA (Table 4). LET exposures in HSCT recipients given 480 mg IV LET were similar to healthy participants given the same regimen. However, exposures in HSCT recipients following oral dosing of LET was lower than healthy participants given the same regimen, which may be attributed to gastrointestinal mucosal injury, reported as a common side-effect of chemotherapy in HSCT recipients, and a similar effect is also anticipated in pediatric HSCT recipients.

Table 4 Predicted Letermovir AUC (ng.hr/mL) Values in Adult HSCT Recipients

Group/Subgroup	Median AUC [a] (ng.hr/mL)	90% Prediction Interval
480 mg Oral, no CsA	34,400	(16,900-73,700)
480 mg IV, no CsA	100,000	(65,300-148,000)
240 mg Oral, with CsA	60,800	(28,700-122,000)
240 mg IV, with CsA	70,300	(46,200-106,000)

AUC=area under the concentration-time curve; CI=confidence interval: CsA=cyclosporin A; HSCT=haematopoietic stem cell transplantation; IV=intravenous.

Overall Median AUC (90% CI) = 49,200 (26,900 – 87,400) ng.hr/mL.

[a] Values are rounded to 3 significant digits.

Exposure-response analyses for efficacy indicated that the entire range of exposures achieved with LET 480 mg QD, adjusted to 240 mg QD LET with CsA coadministration, in the Phase 3 study (P001) is efficacious. There was no significant dependence of the efficacy endpoint (proportion of participants with CS-CMVi) on LET exposures over the range of exposures assessed using exposure quartiles. The exposure-safety analyses showed that there was no exposure dependency for the selected AEs over the exposure ranges achieved in the Phase 3 study.

A PBPK model was developed for exploring the basis of differences in LET PK between populations, including adult and pediatric. The PBPK model incorporated key absorption, distribution, metabolism, and excretion (ADME) and PK properties of LET such as biliary excretion as the major route of elimination, saturable UGT-mediated metabolism, and CYP3A-mediated metabolism as a minor pathway.

A full PBPK model with first-order absorption and a permeability-limited liver model were applied to describe the distribution of LET. The final model successfully described the key plasma disposition properties of LET including the nonlinear PK and the magnitude of greater-than-dose-proportional increase in exposure in white healthy volunteers. The mechanism of nonlinear PK was best described by the saturation of OATP1B-mediated hepatic uptake transporter and was most sensitive towards changes in Michaelis-Menten parameters of OATP1B transporter.

Both the adult Phase 3 population PK model and adult PBPK model with pediatric module were used to predict exposures to support initial dose selection in the pediatric population, as described in Section 4.3.

2.2.4 Preclinical and Clinical Studies

In animal studies, LET was not shown to be genotoxic. Complete details of additional preclinical studies (including repeat dose-toxicity studies in rats [Barrow, P. C., et al 2011] and monkeys [Barrow, P. C., et al 2011] and fertility and embryo-fetal development study in

rats [Barrow, P. C., et al 2011]) can be found in the accompanying IB. These studies support the evaluation of LET in the pediatric population.

LET has been shown to be generally well tolerated in 29 Phase 1 studies, 1 biopharmaceutic study evaluating the oral granule formulation (P031, described below), 2 Phase 2 clinical studies (P019 and P020) and a single, pivotal Phase 3 study (P001) conducted in adult HSCT recipients. Proof-of-concept (antiviral activity) was established in the Phase 2a study (P019), while the safety and efficacy of LET for CMV prophylaxis in HSCT recipients was demonstrated in a dose-dependent manner in the Phase 2b study (P020). The results of the pivotal Phase 3 study (P001) established the safety and efficacy of LET for CMV prophylaxis in adult CMV-seropositive recipients (R+) of an allogeneic HSCT. These studies are described in greater detail in the accompanying IB.

Comparative Bioavailability Study of LET Oral Pediatric Formulations (P031)

P031 evaluated the comparative bioavailability of 2 different LET pediatric oral granule formulations (2 x 120 mg; an Opadry® coating, and an Opadry + Surelease® coating), compared with the currently marketed adult tablet (240 mg) (in n=24 healthy adults). For each pediatric formulation, a subset of 6 participants was randomized to coadministration with either applesauce or vanilla pudding. The PK profiles of both pediatric formulations were bioequivalent to the adult tablet. The geometric mean ratios (GMR) and 90% confidence intervals (CI) for AUC0-inf and Cmax of the formulation comparisons are summarized in Table 5. The Opadry-coated granules were selected for the current study following evaluation both of the PK profile of this formulation and of manufacturing considerations. The effect of food on the PK profile of the Opadry-coated granules was assessed as not clinically significant as the 90% CI of the LET AUC GMR (fed / fasted) fell within the clinical comparability range (0.5 to 3.0). Applesauce resulted in a 20% increase in LET AUC and 33% increase in Cmax, while vanilla pudding resulted in a 13% increase in AUC and 25% increase in Cmax. The Opadry coating was also considered to provide advantages in stability and manufacturing. Furthermore, in a palatability assessment, the majority of participants indicated that the oral granules (Opadry coating) mixed in vanilla pudding or applesauce were neutral to very easy to swallow, had a neutral or pleasant taste and texture, and had a neutral or pleasant aftertaste (10 minutes after administration). No safety concerns were observed with LET administration.

Table 5 Summary of the Geometric Mean Ratios and 90% Confidence Intervals for MK-8228 Plasma PK of AUC0-inf and Cmax Following Administration of a Single Oral Dose of 240 mg (2x120 mg) MK-8228 Coated Granule Formulations Administered Alone, in Applesauce, or in Vanilla Pudding Compared With 240 mg Tablet in Healthy Adult Participants

	GMR and 90% CI	
Oral Granule Comparisons	AUC0-inf[a]	Cmax[a]
Granules (2 x 120 mg) vs Tablet (240 mg) fasting		
MK-8228 Granules (Opadry)/MK-8228 Tablet	1.00 (0.95, 1.06)	1.05 (0.97, 1.14)
MK-8228 Granules (Opadry+Surelease)/ MK-8228 Tablet	0.97 (0.90, 1.03)	0.94 (0.86, 1.04)
Granules (2 x 120 mg) mixed with soft food vs Granules alone (2 x 120 mg)		
MK-8228 Granules (Opadry) in vanilla pudding/ MK-8228 Granules (Opadry)	1.13 (1.04, 1.22)	1.25 (1.13, 1.39)
MK-8228 Granules (Opadry) in applesauce/ MK-8228 Granules (Opadry)	1.20 (1.00, 1.43)	1.33 (1.09, 1.63)
MK-8228 Granules (Opadry+Surelease) in vanilla pudding/ MK-8228 Granules (Opadry+Surelease)	1.15 (1.04, 1.28)	1.42 (1.26, 1.61)
MK-8228 Granules (Opadry+Surelease) in applesauce/ MK-8228 Granules (Opadry+Surelease)	1.10 (0.99, 1.23)	1.15 (1.01, 1.31)

CI=Confidence interval; GMR=Least-squares Geometric Mean Ratio between treatments; MK-8228=letermovir (LET).

[a] Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

2.2.5 Ongoing Clinical Studies

Refer to the IB for further details on the ongoing studies.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

There are no hypotheses to be tested in this study.

In pediatric (birth to <18 years of age) participants who received an allogeneic HSCT and are at risk for CMV infection and/or disease:

Objectives	Endpoints
Primary	
• Objective: To evaluate letermovir PK in pediatric participants grouped by age.	• AUC0-24, Cmax (for participants receiving oral formulation), Ceoi (for participants receiving IV formulation), and Ctrough
Secondary	
• To evaluate the safety and tolerability of treatment with letermovir through Week 48 post-transplant based on the proportion of participants with adverse events.	• Adverse Events (AEs) • AEs Resulting in Study Medication Discontinuation
• To evaluate the efficacy of letermovir in prevention of clinically significant CMV infection through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant.	• Clinically significant CMV infection (CS-CMVi, defined as initiation of preemptive therapy [PET] for documented CMV viremia and/or CMV disease)
• To evaluate the palatability and acceptability of treatment with letermovir oral granules.	• Score on a palatability scale

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2b, open-label, single-arm study to evaluate PK, safety, tolerability, and efficacy of LET when used for CMV prophylaxis in pediatric participants from birth to less than 18 years of age who are at risk of developing CS-CMVi following an allogeneic HSCT.

Clinically significant CMV infection is defined as the occurrence of either one of the following outcomes:

- onset of CMV end-organ disease,

and/or

- initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the participant.

Approximately 60 HSCT recipients will be enrolled in this study. Only R+ participants will be enrolled in the oldest age group (Age Group 1, see below). CMV seroprevalence decreases with decreasing age. Therefore, enrollment criteria for Age Groups 2 and 3 have been broadened to include participants with any risk for CMV reactivation (ie, R+ and/or D+; Section 5.1).

Screening of participants may begin 15 days prior to transplantation, but enrollment must occur no later than 28 days post-transplant (Figure 1). Participants will be tested for CMV viremia using a CMV DNA PCR assay. After establishing absence of CMV viremia, participants will be tested once a week in order to minimize enrollment of those with active CMV replication in the study. Any participant who tests positive for CMV viremia prior to enrollment will be excluded from the study.

On the day of enrollment, eligibility criteria should be confirmed. Participants should have no documented CMV viremia as confirmed from a sample collected within 5 days prior to enrollment. Creatinine clearance and liver function test results within 5 days prior to enrollment should be within the range allowable as outlined in Section 5.2. Once enrolled, CMV viremia will be monitored at the time intervals detailed in the Schedule of Activities (SoA; Section 1.3). LET prophylaxis (study intervention) may begin as early as the day of transplant and will continue through Week 14 (~100 days) post-transplant.

The study will enroll (allocate to receive LET) participants in 3 Age Groups:

- Age Group 1: From 12 to <18 years of age (adolescents)
- Age Group 2: From 2 to <12 years of age (children)
- Age Group 3: From birth to <2 years of age (neonates, infants, and toddlers)

See Figure 2 and Table 6 for distribution of study participants by age groups and panels.

Enrollment will begin with Age Group 1 and move sequentially to younger age groups based on evaluation of PK in Panel A of the preceding age group (Figure 2). For Age Group 1 and Age Group 2, an initial small cohort of participants (Panel A, n=6 participants) will be evaluated prior to enrolling more participants in the same age group (Panel B, n=20).

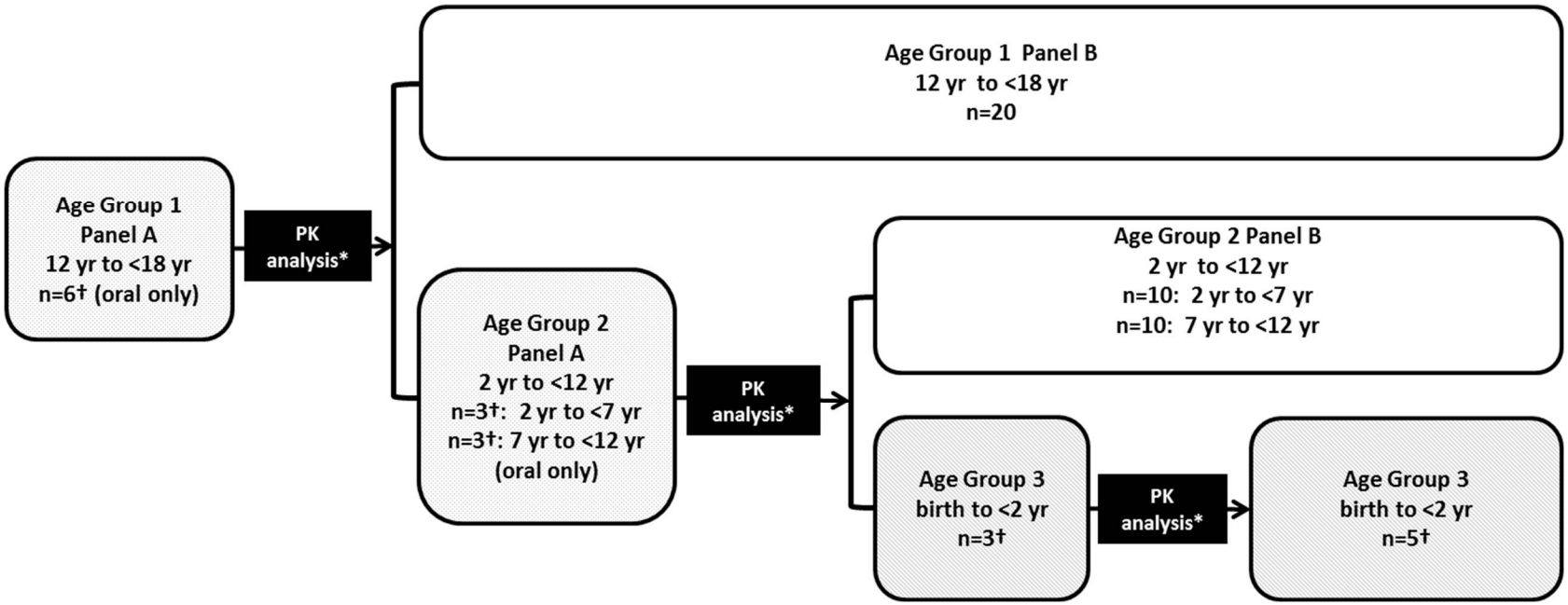
For Age Group 2, approximately half of the enrolled participants will be 7 to <12 years of age; the remainder will be from 2 to <7 years of age. This will allow for the assessment of maturation effects on the PK disposition of LET, ensure a wide age and weight distribution representative of the entire age group, and will provide continuity of the age and weight distributions with Age Groups 1 and 3.

Age group assignment is based on the age at the time of documented informed consent/assent.

Panel A will examine the PK to identify the correct dosing for an age group. Non-compartmental analysis of PK parameters will be performed, population PK and PBPK models will be updated as necessary, and optimal doses confirmed for further study. The final dose selected in Panel A will trigger initiation of Panel B in the same age group, and Panel A in the younger age group, simultaneously. In the event that the PK exposure results from Panel A suggest the dose should be modified, any participant remaining on LET in Panel A will have their dose adjusted for the remainder of the treatment period. All participants that enroll in Panel B will receive the modified dose. Recommendations for dose modifications will be communicated to sites via a Protocol Clarification Letter (PCL) as soon as they are available.

Due to anticipated enrollment challenges (few HSCTs performed and low CMV seroprevalence), there will be only 1 panel (n=8) for the youngest age group (Age Group 3). Enrollment in this panel will be temporarily held after 3 participants are enrolled for further PK analysis to confirm dosing prior to continuing enrollment in this age group. The dose for the remaining participants (n=5) will be confirmed or modified by the Sponsor once the results of this PK analyses are available. The recommended dosing for each age group will be confirmed or modified by the Sponsor after each PK analysis.

Figure 2 Sequential Evaluation of Age Groups



PK=pharmacokinetics; yr=year.
† n represents number of PK-evaluable participants.
* PK analysis will occur at 3 intervals: when all evaluable participants have completed intensive PK in Age Group 1 Panel A, when all evaluable participants have completed intensive PK in Age Group 2 Panel A, and when the first 3 evaluable participants have completed intensive PK in Age Group 3.

LET formulations: Oral and IV formulations of LET will be available (Section 6.1). LET should preferably be initiated as an oral formulation (tablets or oral granules), as long as the participant is able to swallow or receives oral granules via a gastric (G) tube or a nasogastric (NG) tube and does not have a condition that may interfere with the absorption of oral medication (eg, vomiting, diarrhea, or a malabsorptive condition). Age Group 1 participants preferably should be administered the tablet formulation; participants unwilling to or unable to swallow the tablet should receive the oral granules by mouth, instead. Instructions for preparation and administration of all LET formulations are provided in the Pharmacy Manual.

As the primary objective of this study is to obtain PK data to support dosing recommendations for the pediatric oral granule formulation, **all participants in Panel A of Age Groups 1 and 2 (and preferably all participants in Age Group 3) must receive an oral formulation from Day 1 through the Day 7 visit when intensive PK sampling is completed**. Panel A participants who need to be switched to the IV formulation during the first 7 days may be switched; they will continue in the study, but will not have intensive PK samples drawn on the Day 7 visit. The Sponsor should be notified immediately, as an additional participant may subsequently be enrolled in the corresponding panel, at the Sponsor's discretion (Section 8.11.2.2).

The IV formulation should only be used when participants are either unable to swallow/cannot use a G tube/NG tube or have a condition that may interfere with the absorption of an oral formulation. Use of the IV formulation should generally be limited to 4 weeks or less in duration. However, it will be left to the investigator's discretion to continue IV administration beyond 4 weeks if the benefit/risk ratio supports continued administration. Simultaneous use of IV and oral LET is **not** allowed. The IV formulation should be switched to oral LET as soon as the condition necessitating the use of the IV formulation resolves.

Cyclosporin A coadministration: In clinical DDI studies in adult participants, coadministration of CsA results in an approximately 2 to 3-fold increase in LET exposures, necessitating lower doses of LET when coadministered with CsA (Section 2.2.3.2). The appropriate dosage of LET for pediatric participants will be first assessed in the absence of CsA (Panel A) to build upon the PK model used for dose selection prior to adding an additional covariate. Table 6 summarizes the enrollment requirements for LET formulation and CsA use as well as the PK sampling requirements by age group and panel.

Table 6 Enrollment Requirements and Pharmacokinetic Sampling by Age Group

Age Group	Age Range	Panel A	Panel B
1	12 to <18 years	• N=6 (PK evaluable) • Participants must receive oral formulation of LET (tablets preferably, or oral granules [a]) from Day 1 through Day 7 visit. • Participants cannot receive concomitant CsA. • Sparse and intensive PK sampling in all participants	• N=20 participants • Participants may receive tablets or oral granules and/or IV formulations of LET. • Participants may receive concomitant CsA • Sparse PK sampling in all participants. Additionally, intensive PK if participant receives at least 5 consecutive days of IV LET[b].
2	2 to <12 years	• N=6 (PK evaluable) - N=3 participants 2 years to <7 years - N=3 participants 7 years to <12 years • Participants must receive **Oral granules** of LET [a] from Day 1 through Day 7 visit. • Participants cannot receive concomitant CsA. • Sparse and Intensive PK sampling in all participants	• N=20 participants - N=10 participants 2 years to <7 years - N=10 participants 7 years to <12 years • Participants may receive oral granules and/or IV formulation of LET. • Participants may receive concomitant CsA. • Sparse PK sampling in all participants. • Intensive PK, if participant receives at least 5 consecutive days of IV LET.
3	birth to <2 years	• N=8 (PK evaluable) • Participants can receive oral granules (preferably) and/or IV formulation of LET. • Participants may receive concomitant CsA. • Sparse PK sampling in all participants • Intensive PK sampling in all participants, regardless of whether on oral or IV LET formulation[b] • HPCD PK sampling[c]	

Age Group	Age Range	Panel A	Panel B
CsA=cyclosporin A; IV=intravenous; HPCD=hydroxypropyl-beta-cyclodextrin; LET=letermovir; n=number of participants; PK=pharmacokinetics. [a] For Age Group 1, tablets should be preferably administered unless the participant is unable or unwilling to swallow the tablet, in which case, the participant may receive oral granules. The oral granules may be administered either by mouth or via a G tube/NG tube, provided the participant does not have a condition that may interfere with the absorption of oral medication (eg, vomiting, diarrhea, or a malabsorptive condition) [b] Intensive PK on IV formulation will be collected from participants who have not had intensive PK on the oral formulations (oral granules/oral tablet); sample collection will start on the 5th consecutive day of IV dosing. [c] HPCD PK sampling will start on the 4th consecutive day of IV dosing. HPCD PK sampling timepoints and additional creatinine clearance monitoring requirements are detailed in Sections 8.6.2 and 8.6.2.1.			

PK sampling: Intensive PK sampling for LET will be done at the Day 7 visit in all Panel A participants who received an oral formulation from Day 1 through Day 7. Panel B participants, and participants who are not on the oral formulation through Day 7 (ie, switch to IV during this period) will not undergo intensive PK sampling on Day 7.

Any participant who receives IV LET for 5 or more consecutive days will have intensive PK sampling performed on the fifth day of IV LET administration, except for those who have already had intensive PK sampling done on the oral formulation. No participant will have intensive PK draws more than once.

All participants in Age Group 3 will have intensive PK sampling done regardless of the formulation received (starting on either the fifth consecutive day of IV LET or the seventh consecutive day of oral LET, whichever comes first).

The Sponsor should be notified if intensive PK cannot be done in a participant in Panels A of Age Groups 1 and 2, and all of Age Group 3. Enrollment of participants in these panels will continue until the minimum number of evaluable participants for the interim PK analyses are enrolled in each panel. After a pause in enrollment for each interim PK analysis, enrollment of additional study participants will be resumed.

Sparse PK sampling will be done in all study participants at the designated visits (Section 1.3–SoA).

HPCD PK sampling: Whole blood will be collected from Age Group 3 participants starting on the fourth consecutive day of IV LET administration. Sections 8.6.2 and 8.6.2.1 contain details on timepoints for HPCD PK sampling and the additional creatinine clearance monitoring requirements for Age Group 3 participants for whom HPCD PK sampling will be obtained.

Monitoring for CS-CMVi: All participants will receive LET from the day of enrollment (Day 1) through Week 14 (~100 days) post-transplant, the period of highest risk for CMV reactivation, with the intent of preventing CS-CMVi. Participants will have study visits

scheduled at weekly intervals during the treatment period. Thereafter, CMV viremia will be monitored every 2 weeks through Week 24 post-transplant, as the risk for CMV reactivation is considerably reduced during this interval. The incidence of CS-CMVi will also be assessed through Week 24 (~6 months) post-transplant to evaluate the occurrence of late CS-CMVi (between Weeks 14 and 24 post-transplant).

For participants who develop CS-CMVi through Week 24 post-transplant, the participant should have a CMV Infection Visit. At this visit, LET should be discontinued (if applicable) and all procedures as outlined in the SoA (Section 1.3), including collection of a CMV DNA PCR sample, should be performed **immediately prior** to the initiation PET or treatment of CMV disease. Such participants will continue to be followed in the study and complete all remaining study visits).

Participants who discontinue the study prior to Week 24 post-transplant should complete an Early Study Discontinuation Visit and complete all procedures as per the SoA (Section 1.3).

Following completion of the study period at Week 24 (~6 months) post-transplant, all study participants will remain in the study for an additional 24 weeks through Week 48 post-transplant for long-term follow-up to continue collecting safety information (Section 8.4). Mortality data will be collected throughout the participants' enrollment in the study.

Following the conclusion of this study and the Clinical Study Report (CSR) for the study, a final PK model will be developed that includes all PK data from participants from birth to 18 years, in addition to relevant adult data previously collected in the program. The final model and proposed pediatric dosing regimen will be summarized in a separate modeling report.

An independent external Data Monitoring Committee (DMC) will be established for safety evaluation. The DMC will review safety data (at proposed time points outlined in Section 9.7 and detailed in the DMC charter), consider the overall risk and benefit of continuing the study to study participants, and make a recommendation to the Sponsor to continue, modify, or end the study. Some analyses may be combined at the request of the DMC. The DMC may review safety data at other time points (including after the last scheduled safety check) as needed.

An independent, Clinical Adjudication Committee (CAC) will be established for adjudicating all potential investigator-reported cases of CMV end-organ disease, as defined in Appendix 8, throughout the study. For analysis purposes, the adjudication of cases by the CAC will take precedence over the investigator's assessment.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Pharmacokinetic Endpoints

The primary objective of this study is to evaluate the PK of LET in pediatric participants to support LET dose selection for use in prevention of clinically significant CMV infection in pediatric patients receiving an allogeneic HSCT. For the noncompartmental analysis (NCA), the primary PK endpoints for LET are: area under the concentration-time curve for the dosing period (AUC0-24), maximum concentration observed (Cmax, for participants receiving oral formulations), minimum concentration observed before next dose (Ctrough), and concentration at the end of infusion (Ceoi, for participants receiving IV formulation). Additional PK parameters for participants receiving oral formulations are time to maximum observed plasma drug concentration (Tmax), half-life (t1/2), apparent clearance (CL/F), and apparent volume of distribution (Vd/F). Additional PK parameters for participants receiving IV formulation are half-life (t1/2), clearance (CL), and volume of distribution (Vd). Plasma samples for PK evaluations will be collected at the time points described in the SoA (Section 1.3). Refer to Section 8.6.1 for the PK sampling scheme.

4.2.1.2 Safety Endpoints

Safety and tolerability are key secondary objectives of this study. The safety and tolerability of LET will be assessed by a clinical evaluation of adverse experiences and evaluation of other study parameters including vital signs, physical examination, 12-lead ECGs, and standard laboratory safety tests at appropriate time points as specified in the SoA (Section 1.3).

Rationale for Specific Safety Endpoint Analyses:

Renal function

The IV formulation of LET contains the excipient HPCD, which can accumulate in patients with renal insufficiency. In this regard, cyclodextrin is also an excipient in other approved IV agents, including IV voriconazole (given with the excipient, sulfobutylether-β-cyclodextrin). Recent data suggest that, despite accumulation of cyclodextrin in patients with reduced renal function, baseline renal function is not a predictor of worsening renal function in patients receiving IV voriconazole [Neofytos, Dionissios, et al 2012]. Additionally, the quantity of cyclodextrin in the IV formulation of LET is less than that in the IV voriconazole formulation (1800 mg of cyclodextrin/vial for a 240-mg dose of LET as compared with 3200 mg of cyclodextrin/vial for a 200-mg dose of voriconazole, which is administered twice a day).

The IV formulation of LET was used in a total of 99 participants (27%) in the pivotal Phase 3 study (P001). The extent of exposure to IV LET was similar to IV placebo in P001. The incidence of AEs reported in recipients of the IV formulation was comparable in the 2 treatment groups. Further assessments of trends in blood urea nitrogen (BUN) and serum

creatinine confirm that the use of the LET IV formulation had a similar renal safety profile compared with placebo, suggesting that the use of the cyclodextrin formulation in P001 was not associated with renal toxicity.

Renal function will be closely monitored in this study (reported AEs as well as laboratory parameters of renal function including BUN, serum creatinine levels and creatinine clearance) to confirm the cyclodextrin-containing IV formulation is not associated with renal toxicity in the pediatric population. Additionally, HPCD PK sampling will be done in Age Group 3 participants who receive the IV formulation for at least 4 consecutive days. See Section 8.6.2 and Section 8.6.2.1 for sampling timepoints and additional creatinine clearance monitoring requirements in these Age Group 3 study participants receiving the IV formulation.

Based on the above, the use of IV LET is permitted in participants in this study with renal insufficiency, provided creatinine clearance is >10 mL/min as calculated by the Cockcroft-Gault equation (for participants ≥12 years of age) or >10 mL/min/1.73 m^2 by the modified Schwartz equation (for participant <12 years of age) or the participant is not on hemodialysis (Appendix 12). However, the IV formulation should only be used when participants are either unable to swallow or have a condition (eg, vomiting, diarrhea, or malabsorptive condition) that may interfere with the absorption of the oral formulation. Participants on IV LET should be switched to the oral formulation as soon as they are able to swallow and/or the condition that warranted the use of the IV formulation has resolved.

4.2.1.3 Efficacy Endpoints

The efficacy endpoints of the study will be the proportion of participants with CS-CMVi through Week 14 (~100 days) and Week 24 (~6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- onset of CMV end-organ disease

  OR

- initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the participant. Initiation of PET in this study refers to the practice of initiating therapy with the following anti-CMV agents when active CMV viral replication is documented: ganciclovir, valganciclovir, foscarnet, and/or cidofovir.

Note: Documented viremia is defined as *any* **detectable** CMV viral DNA (including PCR results above or below the lower limit of quantification).

CMV infection, as measured by CMV viremia, is associated with considerable morbidity and mortality in HSCT recipients due to an increased incidence of CMV disease (the “direct” effects) and the “indirect” effects secondary to the effects of CMV on the immune system as described in Section 2.2.

Currently, with most centers using PET for prevention of CMV disease, the overall incidence of CMV disease in HSCT recipients has declined to around 5% in the first 3 months

post-transplant, the period of highest risk, from 20% to 30% prior to the routine use of preventive measures [Boeckh, M. 2011] [Boeckh, M. and Nichols, W. G. 2004] [Marty, F. M., et al 2011] [Craddock, C., et al 2001] [Boeckh, M., et al 1992] [Winston, D. J., et al 2008] [Ljungman, P., et al 1998] [Snydman, D. R. 2011]. Therefore, the efficacy endpoint selected for this study – CS-CMVi – will be a composite endpoint of CMV infection warranting initiation of PET and/or CMV disease.

Assessment of Efficacy Endpoint

Detection of CMV in plasma or blood is associated with an increased risk of CMV disease [Gerna, G., et al 2011] [Lowance, D., et al 1999] [Gor, D., et al 1998] [Atkinson, C. and Emery, V. C. 2011]. CMV viral DNA as a measure of CMV infection is already used routinely in clinical practice to initiate and monitor PET [Boeckh, M. 2011] [Boeckh, M. and Ljungman, P. 2009] [Winston, D. J., et al 2008] [Härter, G. and Michel, D. 2012] [Emery, V. C., et al 2000]. The decision to initiate PET should be guided by detection of viral DNA and the clinical condition of the participant.

Investigators will report all "probable" and "proven" cases of CMV disease using the definitions in Appendix 8. All investigator-reported disease will be confirmed by an independent CAC. The CAC will review clinical, virological, and histopathological data as well as the investigator's assessment for adjudicating all potential cases of end-organ CMV disease. For analysis purposes, the adjudication of cases by the CAC will take precedence over the investigator's assessment.

4.2.1.4 Palatability and Acceptance Assessment Endpoint

Palatability may play an important role in adherence to treatment in the pediatric population. Palatability is an important element in the determination of acceptability, and encompasses a product's smell, taste, aftertaste, and texture. Acceptability, including palatability, of the oral granule formulation will be assessed in all participants using the Palatability Acceptance Assessment (PAA). In previous studies, the most commonly reported assessment measured palatability preference using a visual analog scale that was modified by including a facial hedonic scale (FHS; facial expression scale depicting various degrees of pleasure) [Thompson, C., et al 2015]. The 5-point FHS for taste is one of the most frequently reported types of palatability assessments used in pediatric clinical studies and will be used in this study.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study intervention(s), the disease under study, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in (Appendix 6).

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

Table 7 and Table 8 show doses for initiating LET prophylaxis with the oral or IV formulations of LET, respectively, when LET is administered with or without CsA, for Age Groups 1 to 3. Age Group 1 (age 12 to <18 years), Panel A started with the adult dose of 480 mg once daily. For Age Group 2 (age 2 to <12 years), the LET doses shown are the starting doses. The starting doses for Age Groups 1 and 2 were confirmed based on the review of interim analyses of PK, safety, and tolerability from Age Group 1, Panel A. Doses for Age Group 3 (birth to <2 years) are based on the accumulated PK, safety, and tolerability data from Age Group 1 (Panels A and B) and Age Group 2 Panel A. The LET doses shown for Age Group 3 in Table 7 and Table 8 are the starting doses and will be confirmed or modified based on the review of an interim analysis of PK, safety, and tolerability from the first 3 participants from Age Group 3. (**Note: for weight-based dosing, weight recorded at enrollment [Day 1] will be used to determine initial dosing. Dose may need to be adjusted according to the most recent body weight taken per the SoA**). In the event the starting doses listed here need to be modified, this information will be communicated to investigators and sites via a PCL. The rationale for these starting doses is described below in Section 4.3.1.1. See Section 6.1 for full dosing instructions.

Participants requiring IV administration or coadministration with CsA within the first 7 days of the study will not be enrolled in Age Groups 1 or 2 of Panel A in order to first establish the oral LET pediatric PK profile and subsequent model predictions. However, participants initially enrolled in Panel A, but requiring a switch to IV administration after the Day 7 visit will still be included in the population PK analysis.

Table 7 Oral Letermovir Dosing Table

Age Group	Age Range	BW limits (kg)	Oral dose LET (mg)	Oral dose LET (mg) with CsA
1	12 to <18 years	Any weight	480	240
2	2 to <12 years	≥30	480	240
		18 to <30	240	120
		10 to <18	120	60
3	birth to <2 years	10 to ≤15	120	60
		7.5 to <10	120	60
		5.0 to <7.5	60	40
		2.5 to <5.0	40	20

BW = body weight recorded at enrollment (Day 1) will be used to determine the initial dosing. Dose may be adjusted according to the most recent body weight taken per the SoA. CsA = Cyclosporin A; IV = intravenous; LET = letermovir; PK = pharmacokinetics; SoA=Schedule of Activities.

Table 8 Intravenous Letermovir Dosing Table

Age Group	Age Range	BW limits (kg)	IV dose LET (mg)	IV dose LET (mg) with CsA
1	12 to <18 years	Any weight	480	240
2	2 to <12 years	≥30	240[a]	240[b]
		18 to <30	120[a]	120[b]
		10 to <18	60[a]	60[b]
3	birth to <2 years	10 to ≤15	60[a]	60[b]
		7.5 to <10	60[c]	60[b,c]
		5.0 to <7.5	40[c]	40[b,c]
		2.5 to <5.0	20[c]	20[b,c]

BW=body weight recorded at enrollment (Day 1) will be used to determine the initial dosing. Dose may be adjusted according to the most recent body weight taken per the SoA; CsA=Cyclosporin A; IV=intravenous; LET=letermovir; PK =pharmacokinetics; SoA=Schedule of Activities.

[a] Based on modeling, for Age Group 2, the IV dose of LET is reduced by 50% compared with oral LET in order to maintain target exposures.
[b] No further reduction of IV LET is necessary when coadministered with CsA.
[c] Based on interim analyses results, doses are increased for participants weighing <10 kg in Group 3

4.3.1.1 Dose Justifications

Using modeling and simulation in the adult clinical program, the relationship between LET exposure and response (efficacy and safety) in adult HSCT recipients was characterized. In addition, the pathogenesis of CMV infection (viremia) and disease, and the mechanism of action of LET, are not anticipated to be different in pediatrics compared with adults. Thus, achieving LET exposures in pediatric HSCT recipients that are similar to adult HSCT recipients is expected to result in similar efficacy and safety in both populations.

Exposure targets:

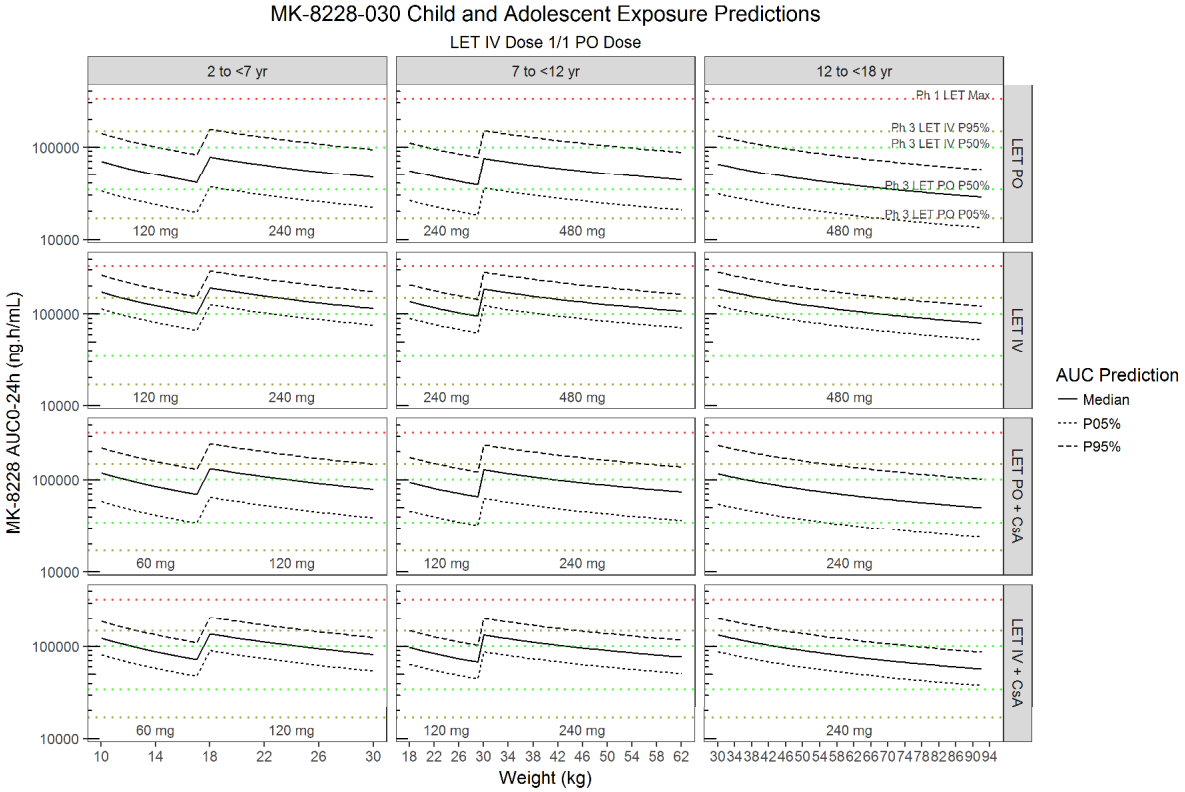
Exposure targets and bounds for the pediatric HSCT population were established using the typical exposures and ranges predicted for the HSCT adult population given the clinical dose. The Phase 3 population PK model predicted steady-state median exposures (AUC0-24h) in adult HSCT recipients following oral and IV LET 480 mg without CsA (Table 4), respectively, were chosen as the target range (34,400 to 100,000 ng.hr/mL) for the pediatric median exposures. In addition, the 5th percentile exposure following 480 mg oral LET, and the 95th percentile exposure following 480 mg IV LET, respectively, were chosen as the (16,900 to 148,000 ng·hr/mL) lower and upper bound for the pediatric exposure range.

Simulations with both the PBPK model combined with the Simcyp pediatric module and the Phase 3 population PK model with allometric scaling were used to select optimal LET doses and weight bounds within each of the 3 age groups, with the goal of keeping both the median and extreme predicted exposures within the prespecified bounds. The pediatric patients had an assumed weight distribution at each age according to CDC (2 to 17 years) and WHO (0 to 23 months) growth tables. Figure 3 and Figure 4 are based on the adult population PK model and depict the predicted pediatric AUC in Age Groups 1 and 2, as a function of Age Group and body weight, for the 4 regimens of oral or IV route of LET administration, and with or without concomitant CsA. Figure 3 is the dosing paradigm using oral and IV LET (without CsA) interchangeably for both Age Groups 1 and 2.

Figure 4 shows the dosing paradigm for this study, where participants in Age Group 2 (2 to <12 years) without coadministration of CsA require a 50% reduction in LET IV dose relative to oral.

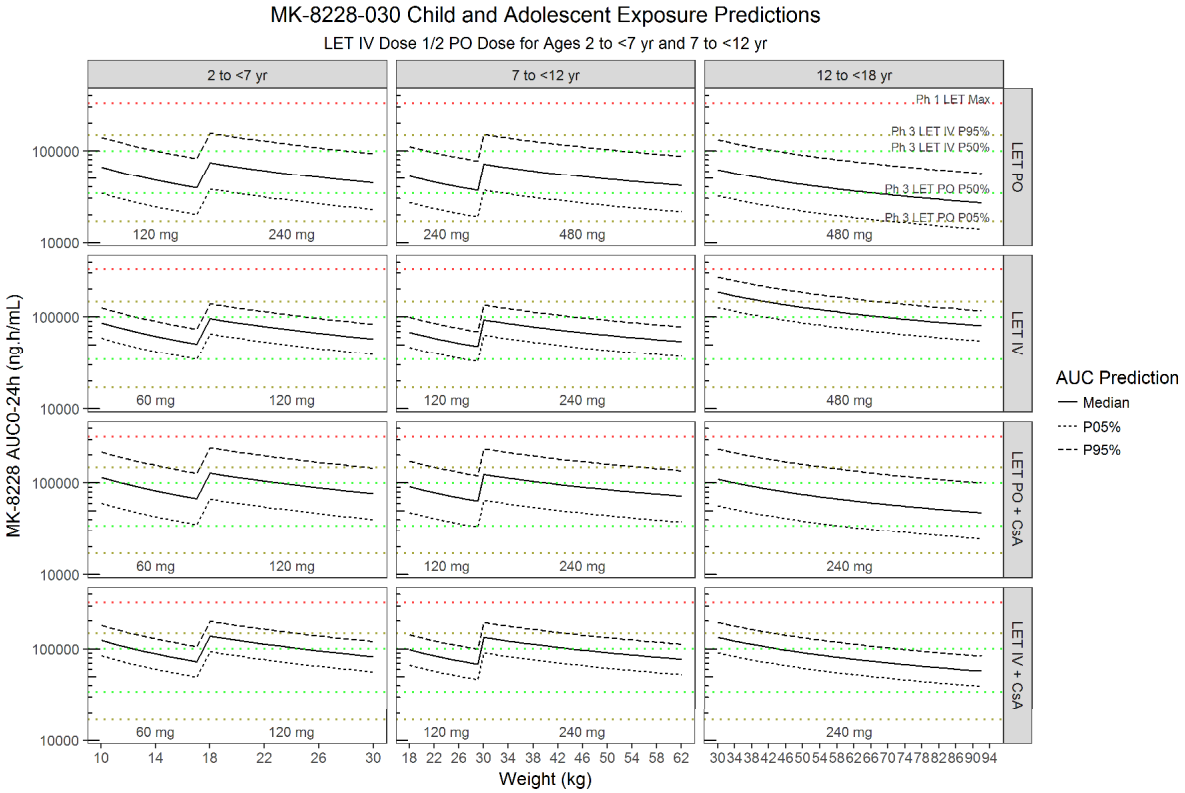
Figure 5 shows the Age Group 3 LET exposure predictions corresponding to the initial dosing paradigm, based on the Phase 3 population PK model with allometric scaling.

Figure 3 LET Median AUC (With 5th and 95th Percentile Prediction Intervals) by age Group and Weight, Based on the Phase 3 Population PK Model With Allometric Scaling. Age Group 1 (12 to <18 yrs) and Age Group 2 (2 to <7 yrs and 7 to <12 yrs), Without Coadministration of CsA, are Given LET IV at the Same Dose as Oral



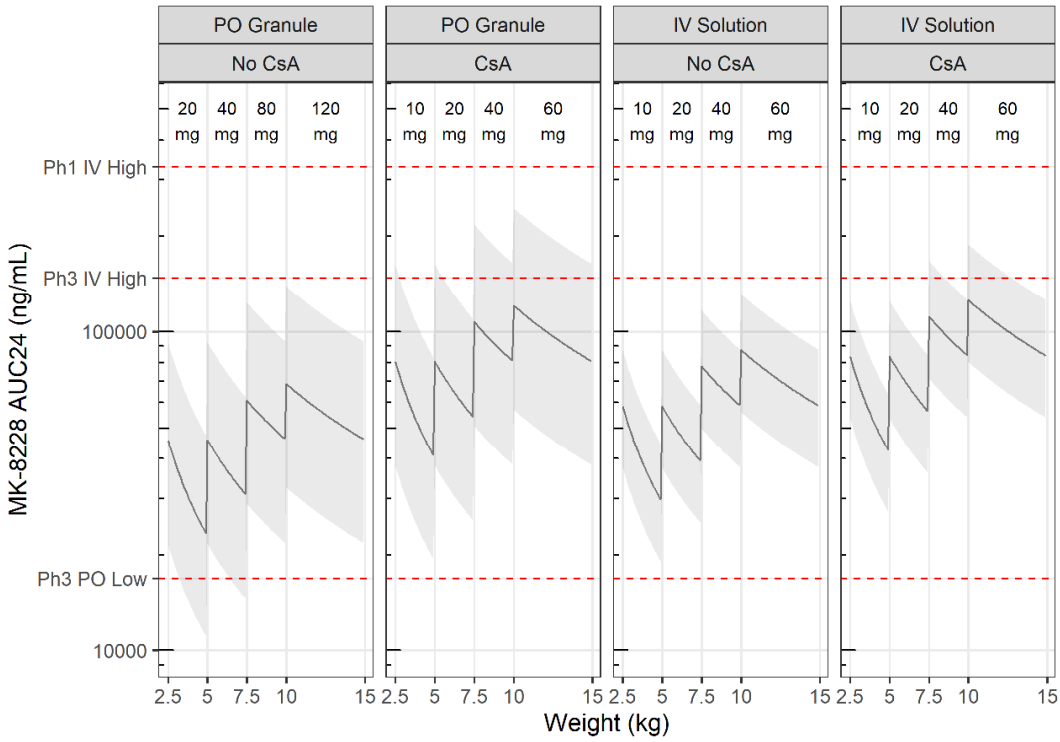
AUC=area under the concentration-time curve; CsA=cyclosporin A; LET=letermovir (MK-8228); IV=intravenous; po=by mouth; yrs=years.

Figure 4 LET Exposure Predictions Corresponding to the Dosing Paradigm for This Study, Showing LET Median AUC (With 5th and 95th Percentile Prediction Intervals) by Age Group and Weight, Based on the Phase 3 Population PK Model With Allometric Scaling. Age Group 2 (2 to <7 yrs and 7 to <12 yrs), Without Coadministration of CsA, has a 50% Reduction in LET IV Dose Relative to Oral



See Table 7 for initial dosing paradigm (oral) and Table 8 for initial dosing paradigm (IV). Green dotted lines are the median exposures (50th percentile) following the 480 mg oral and IV LET dose (without CsA) of 34,400 to 100,000 ng.hr/mL, respectively, and represent the target exposure range for the pediatric median exposures. Brown dotted lines are the 5th percentile exposure of 16,900 ng·hr/mL following 480 mg oral LET and the 95th percentile exposure of 148,000 ng·hr/mL following 480 mg IV LET, and represent the lower and upper bound targets, respectively, for the pediatric exposure range.
Red dotted line is the maximal AUC exposure achieved in the Phase 1 program.
AUC=area under the concentration-time curve; CsA=cyclosporin A; LET=letermovir (MK-8228); IV=intravenous; po=by mouth; yrs=years.

Figure 5 Age Group 3 LET Exposure Predictions Corresponding to the Initial Dosing Paradigm, Showing LET Median AUC (With 5th and 95th Percentile Prediction Intervals) by Weight, Based on the Phase 3 Population PK Model With Allometric Scaling.



Solid lines are medians and shaded regions are 90% prediction intervals.
AUC=area under the concentration-time curve; CsA=cyclosporin; IV=intravenous; Ph=Phase; po=by mouth.

LET is transported by OATP1B1/3, for which limited maturation data are available. In the literature, relative protein expression of OATP1B1 was highly variable among individuals, and no statistically significant difference was observed among the studied age groups [Thomson, M. M., et al 2016] [Prasad, B., et al 2016]. For OATP1B3, protein expression was not significantly different between adults and children >1 year, but was significantly different for children <1 year [Prasad, B., et al 2016]. However, it is unknown how much of the measured protein represents active transporter. Therefore, dose predictions for Age Group 3 (birth to <2 years) exhibit a higher uncertainty than the older pediatric age groups. As such, dose predictions for Age Group 3 were determined by the interim analysis following the availability of Age Group 2 Panel A PK data, along with all cumulative PK, safety, and tolerability data. The resulting oral and IV dose selections for all Age Groups are presented in Table 7 and Table 8, respectively.

LET administered without CsA:

The adult clinical program included patients with a body weight range of 35.1 to 141.5 kg who demonstrated favorable PK, safety, and efficacy. Based on the comparable body weight and OATP1B maturation in participants aged 12 to <18 years (Age Group 1), it is anticipated that the PK of LET in this age group will behave similarly to those of adults receiving the

adult 480-mg oral dose of LET. The adult clinical program supports that the IV and oral LET dose are interchangeable. This approach was modeled for Age Group 1, and although the predicted exposures for IV and/or CsA regimens exceeds the median and upper bound exposure targets for simulated adolescents approaching the lowest 5th percentile weight of 30 kg, the exposures are generally within the target exposures overall, and are below the highest exposure achieved in the entire clinical program (~ 328,000 ng.hr/mL) (Figure 4, rows 2-4, column 3). Exposures in the lowest weight adolescents will be carefully monitored, and an additional weight band in Age Group 1 may be added in the event actual exposures exceed the clinical experience in adults.

During the modeling of the dose selections for Age Group 2, when using interchangeable doses for IV and oral LET, the predicted exposures for IV without CsA exceeded both the median and upper bound exposure targets (Figure 3, row 2, columns 1-2). In order to maintain predicted exposures within target bounds for IV, 2 options for Age Group 2 were considered: (1) add additional weight bands with a narrower weight range and maintain interchangeable IV and oral doses; or (2) maintain the current weight bands and reduce the IV dose by 50%. Given that there is less known about drug disposition in this age group, and that the children with the lowest body weight were at the highest risk to exceed the upper limit of the exposure target, in order to achieve the target exposure range in Age Group 2, the initial IV dose of LET is reduced by 50%.

LET administered with CsA:

As the PBPK models are not currently validated to predict drug-drug interactions for CsA, the Phase 3 population PK model alone was used to estimate LET exposures with CsA, suggesting a reduction of oral LET dose by 50% when given with CsA for ages 2 to <18 years, due to the expected increase in bioavailability and decrease in clearance with CsA. No further reduction in the LET IV dose is anticipated when coadministered with CsA (Figure 3).

4.3.1.2 Dose in Age Group 1 (12 to <18 years), Panel A

For the initial dose for Age Group 1 Panel A, the LET PBPK model simulations assume the same OATP1B1/3 abundance for hepatic uptake and effects of physiology as estimated for adult patients. The PBPK and the population PK model suggests that the adult dose of LET of 480 mg oral or IV will result in comparable exposures in ages 12 to <18 years as in adults. The adult tablets will be used in this age group, thus establishing continuity with the body of adult PK data from the adult studies. For participants unable or unwilling to swallow the adult tablets, oral granules may be used (see Section 6.1 for dosing instructions). No dose modifications for Age Group 1 were necessary based on the interim PK analysis of all evaluable participants in Age Group 1 Panel A.

4.3.1.3 Dose in Age Group 2 (2 to <12 years), Panel A

The doses for Age Group 2 Panel A shown in Table 7 and Table 8 were estimated, as described in Section 4.3.1.2. The doses were confirmed by interim analyses of PK, safety, and tolerability data. Age Group 2 (2 to <12 years) is subdivided into weight bands. For

participants weighing ≥30 kg, an oral dose of 480 mg of LET is estimated to result in comparable exposures as the adult HSCT patients. For participants weighing 18 to <30 kg, an oral dose of 240 mg of oral granules of LET is estimated to result in comparable exposures as the adult HSCT patients. For participants weighing 10 to <18 kg, an oral dose of 120 mg of LET is estimated. In the event that a participant is switched to IV LET, the IV dose is reduced in this age group and the estimated IV doses are described in Table 8.

A minimum of 3 evaluable participants per age range (2 years to <7 years, and 7 years <12 years) are required prior to initiating interim PK analysis, in order to assess maturation effect on the PK disposition of LET. No dose modifications for Age Group 2 were necessary based on the planned interim PK analysis of all evaluable participants in Age Group 2 Panel A.

All participants in Age Group 2 Panel A will receive oral granules sprinkled on soft food or administered via a G tube/NG tube (see supporting study documentation [eg, Pharmacy Manual] for details on preparation and administration of oral granules by mouth or via G tube/NG tube).

4.3.1.4 Dose in Age Groups 1 and 2, Panel B

The doses for Panel B were determined from interim analyses of PK, safety and tolerability following the completion of intensive PK in all participants of Panel A. The interim PK analysis was based on NCA of Panel A intensive PK, and utilized population PK and PBPK modeling and simulation based on all cumulative PK data.

The goal of the interim PK analyses was to assess LET PK in each age group and determine whether exposures are broadly similar to adult HSCT recipients. The Day 7 intensive PK data from Age Group 1 or 2 of Panel A was used to estimate exposures using NCA. The range of exposures estimated by NCA was largely within the limits of those observed for adult therapeutic doses; no adjustments to the doses specified in Table 7 and Table 8 were made for Panel B. The final determination of doses for Panel B was based on the composite assessment of cumulative PK and safety and tolerability results through Panel A.

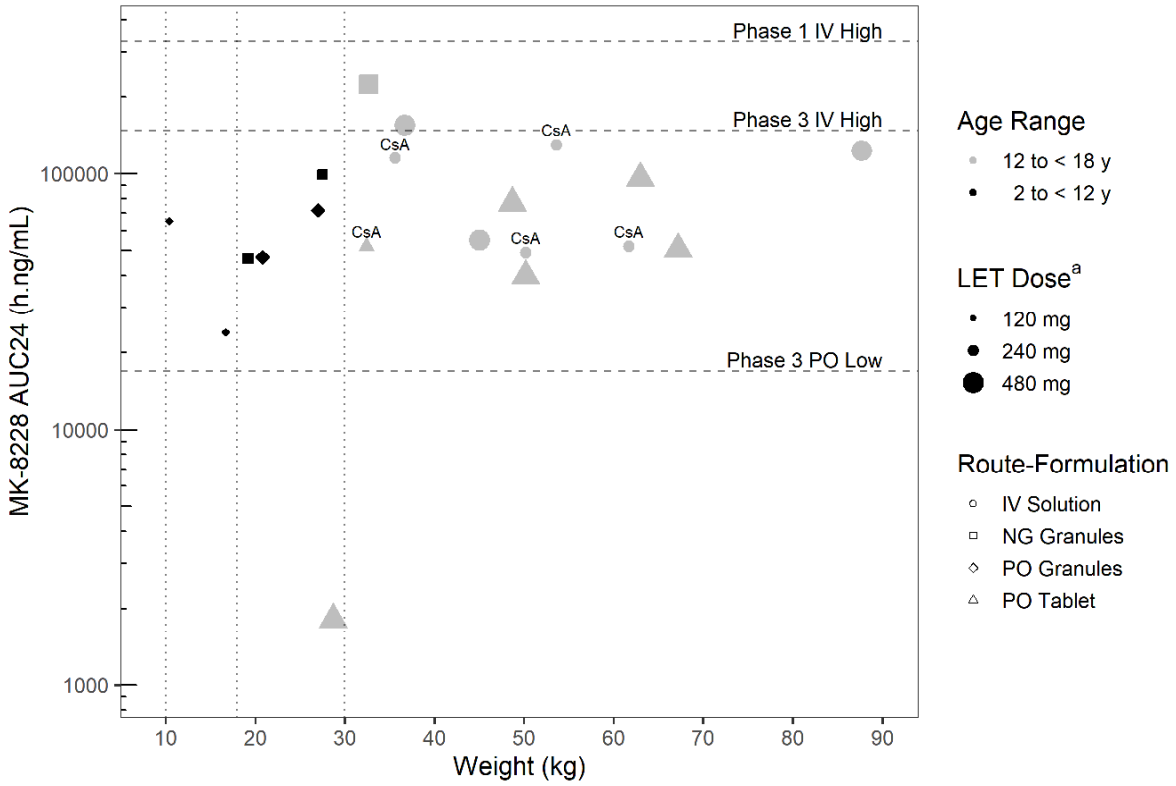
Recommendations for dose modifications will be communicated to investigators and sites via a PCL as soon as they are available. The interim and final analyses will be described in a separate Modeling and Simulation Plan, and reported in separate Modeling and Simulation Reports.

4.3.1.5 Age Groups 1 and 2 Pharmacokinetic Experience Through Interim Analysis 2

The initial dose selections for Age Groups 1 and 2 were evaluated by intensive PK measurements for Panel A (n=6 per Age Group) following oral administration of LET without CsA for at least 7 days. As of the second interim analysis, 7 participants in Age Group 1 Panel B had intensive PK following IV administration of 480 mg LET for at least 5 consecutive days, with 4 of 7 participants coadministered CsA. In addition, 1 participant in Age Group 1 Panel B had intensive PK following oral administration of 240 mg LET with

CsA. Exposures that exceeded the adult exposure target range were also compared with the upper clinical bound of the highest exposure observed in the LET Phase 1 program (328000 h.ng/mL). Figure 6 shows the steady-state exposures (AUC24) determined by noncompartmental analysis (NCA) for the (n=20) participants who had intensive PK as of Interim Analysis 2. Overall, 17/20 participants had exposures in the adult exposure target range, comprising 4/6 participants in Age Group 1 Panel A, 7/8 participants in Age Group 1 Panel B, and 6/6 participants in Age Group 2 Panel A. Of the 3/20 participants who had exposures outside the adult exposure target range, one participant receiving oral LET (Age Group 1 Panel A) had an exposure below the target range, another receiving oral LET (Age Group 1 Panel A) had an exposure above the target range, but 1.46-fold below the upper clinical bound, and one participant receiving IV LET (Age Group 1 Panel B) had an exposure above the target range, but 2.11-fold below the upper clinical bound. Overall, these results support the validity of the method used to determine the doses for Age Groups 1 and 2, and the continuation of the same method for Age Group 3.

Figure 6 Letermovir Exposure (AUC24) in All Participants From Age Groups 1 and 2 who had Intensive PK (N=20)



AUC24=area under the concentration-time curve for the dosing interval (0 to 24 hours); CsA=cyclosporin; IV=intravenous; NG=nasogastric; po=by mouth; y=year.
CsA above the symbol indicates CsA was coadministered with the LET dose. Vertical dotted lines show the dosing weight band boundaries for Age Group 2 (there are no dosing weight boundaries for Age Group 1).
[a] The relative size of each symbol reflects the dose of LET: small=120 mg; medium=240 mg; large=480 mg.

4.3.1.6 Dose in Age Group 3

The initial doses in Age Group 3 were determined based on an analysis of the accumulated PK data from Age Group 1 (Panels A and B) and Age Group 2 Panel A, as described above in Section 4.3.1.4. Having validated the dose selection for Age Groups 1 and 2, the method of allometric scaling of the adult Phase 3 population PK model was applied to Age Group 3. A metabolic maturation adjustment to the allometric scaling coefficient for glucuronidated drug clearance was used, as well as a small adjustment to exposure for granules consumed with food. The Age Group 3 participants have an assumed weight distribution according to WHO (0 to 23 months) growth tables. As for all age groups, doses and weight bands were selected to keep the predicted pediatric exposures within the adult target range. The resulting simulated exposures in Figure 5 show that nearly all Age Group 3 participants are expected to have exposures in the adult target range with the proposed doses in Table 7 and Table 8.

Following the collection of intensive PK in 3 evaluable participants in Age Group 3, enrollment was paused until after the analysis of intensive PK and reevaluation of the initial dose for this age group. Changes in doses for Age Group 3 was communicated to investigators and sites via a PCL.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose of LET in this study will not exceed 480 mg once daily.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent/assent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3).

4.4.1 Clinical Criteria for Early Study Termination

Early study termination will be the result of the criterion specified below:

1. The eDMC recommends termination of the study and the Executive Oversight Committee (EOC) agrees as stated in the DMC charter.

2. The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped, as described in Appendix 10.1.10.

5 STUDY POPULATION

Male and female recipients of an allogeneic HSCT between the ages of birth and <18 years of age (on the day of documenting informed consent/assent) will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, race, ethnicity, and sex. The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

An individual is eligible for inclusion in this study if the individual meets all of the following criteria:

1. All Age Group 1 participants must have documented positive CMV serostatus (CMV IgG seropositive) for the recipient (R+) within 90 days prior to enrollment.

   Participants in Age Group 2 and 3 must have documented positive CMV serostatus (CMV IgG seropositive) for the recipient (R+) within 90 days prior to enrollment and/or for the donor (D+); the donor serostatus should be documented within 1 year prior to enrollment.

2. Be the recipient of a first allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant).

3. Have undetectable CMV DNA from a plasma or whole blood sample collected within 5 days prior to enrollment.

4. Be within 28 days post-HSCT at the time of enrollment.

Demographics

1. Participant is aged from birth to <18 years of age at the time of providing documented informed consent/assent.

Female Participants

2. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:
   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

      OR

   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 28 days after the last dose of study intervention.

Informed Consent/Assent

3. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant or legally acceptable representative may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

4. Study participants in Panel A of Age Groups 1 and 2 must not be on concomitant CsA and must be able to take (as assessed by the investigator) LET tablets or the oral granules (either by mouth or via G tube/NG tube), provided the participant does not have a condition that may interfere with the absorption of oral medication (eg, vomiting, diarrhea, or a malabsorptive condition) from the day of enrollment until the intensive PK sampling is completed in these panels (Day 7 Visit, see SoA, Section 1.3).

5. For Age Group 2, the participant's weight should be at least 10 kg; and for Age Group 3, the participant's weight should be at least 2.5 kg and less than or equal to 15 kg at the time of enrollment.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has received a previous allogeneic HSCT (Note: receipt of a previous autologous HSCT is acceptable).

2. Has a history of CMV end-organ disease within 6 months prior to enrollment.

3. Has evidence of CMV viremia at any time from either providing documented ICF or the HSCT procedure, whichever is earlier, until the time of enrollment. (Note: Evidence of CMV viremia will include any test result reported as "positive" on a qualitative assay; "detectable" including "detectable, not quantifiable," or "detected" with a numeric value provided by a quantitative assay.)

4. Has suspected or known hypersensitivity to active or inactive ingredients of LET formulations.

5. Has severe hepatic insufficiency (defined as Child-Pugh Class C; see Appendix 9) within 5 days prior to enrollment.

6. Has serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 x the upper limit of normal (ULN) or serum total bilirubin >2.5 x ULN within 5 days prior to enrollment.

   Note: Participants who meet this exclusion criterion may, at the discretion of the investigator, have repeat testing done one time prior to enrollment. If the repeat value

does not meet this criterion, they may continue in the screening process. Only the specific out of range value should be repeated (not the entire panel).

7. Is a) on renal replacement therapy (eg, hemodialysis, peritoneal dialysis)

   OR

   b) has end-stage renal impairment with a creatinine clearance ≤10 mL/min, as calculated by the Cockcroft-Gault equation (for participants ≥12 years of age) or ≤10 mL/min/1.73 m^2 by the modified Schwartz equation (for participants <12 years of age) using serum creatinine within 5 days prior to enrollment (Appendix 12).

   Note: Participants who meet this exclusion criterion may, at the discretion of the investigator, have repeat testing done one time within 5 days prior to enrollment. If the repeat value does not meet this criterion, they may continue in the screening process. Only the specific out of range value should be repeated (not the entire panel).

8. Has both moderate hepatic insufficiency AND moderate-to-severe renal insufficiency.

   Note: Moderate hepatic insufficiency is defined as Child-Pugh Class B (Appendix 8); moderate-to-severe renal insufficiency is defined as a creatinine clearance <50 mL/min, as calculated by the Cockcroft-Gault equation (for participants in Age Group 1) or <50 mL/min per 1.73 m^2 calculated using the modified Schwartz equation (for participants in Age Group 2). Participants in Age Group 3 should not be enrolled if they have moderate hepatic insufficiency and creatinine clearance <20 mL/min per 1.73 m^2 calculated using the modified Schwartz equation; see Appendix 12 for Cockcroft-Gault and modified Schwartz equations).

9. Has an uncontrolled infection on the day of enrollment.

10. Requires mechanical ventilation or is hemodynamically unstable at the time of enrollment.

11. Has a documented positive result for a human immunodeficiency virus antibody (HIV-Ab) test at any time prior to enrollment, or for hepatitis C virus antibody (HCV-Ab) with detectable HCV RNA, or hepatitis B surface antigen (HBsAg) within 90 days prior to enrollment.

12. Has active solid tumor malignancies with the exception of localized basal cell or squamous cell skin cancer or the condition under treatment (eg, lymphomas).

13. Has a preexisting cardiac condition a) for which the patient is currently being treated or b) which required hospitalization within the last 6 months or c) that may be expected to recur during the course of the trial. Examples of preexisting cardiac conditions that would preclude enrollment include atrial fibrillation and atrial flutter.

Prior/Concomitant Therapy

14. Received within 7 days prior to enrollment any of the following:

    - ganciclovir
    - valganciclovir
    - foscarnet
    - acyclovir (at doses greater than those recommended for HSV/VZV prophylaxis; see Appendix 10)
    - valacyclovir (at doses greater than those recommended for HSV/VZV prophylaxis: see Appendix 10)
    - famciclovir

15. Received within 30 days prior to enrollment of any of the following:

    - cidofovir
    - CMV immunoglobulin
    - any investigational CMV antiviral agent/biologic therapy
    - Rifampin and other strong inducers (such as phenytoin, carbamazepine, St John's wort (*Hypericum perforatum*), rifabutin and phenobarbital) and moderate inducers such as nafcillin, thioridazine, modafinil and bosentan.

16. Received letermovir at any time prior to enrollment in this study.

Prior/Concurrent Clinical Study Experience

17. Is currently participating or has participated in a study with an *unapproved* investigational compound or device within 28 days, or 5X half-life of the investigational compound (excluding monoclonal antibodies), whichever is longer, of initial dosing in this study. Participants previously treated with a monoclonal antibody will be eligible to participate after a 28-day washout period.

    Note: Investigational chemotherapy regimens involving *approved* agents and investigational antimicrobial regimens involving *approved* antibacterial/antifungal/antiviral agents, investigational radiotherapy studies, or other observational studies are allowed.

18. Has previously participated in this study or any other study involving LET.

19. Has previously participated or is currently participating in any study involving administration of a CMV vaccine or another CMV investigational agent, or is planning to participate in a study of a CMV vaccine or another CMV investigational agent during the course of this study.

    Refer to Section 6.5.2.1 for information on COVID-19 vaccines.

Other Exclusions

20. Is pregnant or expecting to conceive, is breastfeeding, or plans to breastfeed from the time of consent through 28 days after the last dose of study intervention.

21. Is expecting to donate eggs starting from the time of consent through 28 days after the last dose of study intervention.

22. Has clinically relevant drug or alcohol abuse within 12 months of screening that may interfere with participant treatment, assessment, or compliance with the protocol, as assessed by the investigator.

23. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or would be put at undue risk as judged by the investigator, such that it is not in the best interest of the participant to participate in this study.

24. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

When using an allowed concomitant medication, please refer to the pediatric prescribing information of each local product circular for meal and dietary restrictions.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

If a participant enrolled in Panel A of Age Group 1 or 2 or in Age Group 3 discontinues from study intervention or withdraws from the study prior to intensive PK sampling, or is considered not evaluable for intensive PK, a replacement participant may be enrolled in the corresponding panel to ensure n=6 PK-evaluable participants in each Panel A, and n=8 PK-evaluable participants in Age Group 3. Enrollment of replacement participants will be at the discretion of the Sponsor and may occur at any active study site. The replacement participant will be assigned a unique allocation number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies study interventions provided by the Sponsor will be packaged to support enrollment and replacement participants as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 9. In this study, approximately 60 participants will be enrolled in three age groups to receive LET once a day from the day of enrollment (Day 1, within 28 days post-transplant) through 14 weeks (~100 days) post-transplant. Both oral (adult tablet and capsules containing oral granules) and IV formulations of LET will be used in this study. Simultaneous use of IV and oral study therapy is **not** allowed.

Dosing for all age groups will be based on age and most recent weight (SoA 1.3.1). Dosing recommendations for all Age Groups are provided in Table 10 and Table 11.

Country-specific requirements are noted in Appendix 7.

Table 9 Study Intervention

	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration[a]	Regimen/ Treatment Period	Use	IMP/ NIMP/ AxMP	Sourcing
1	Experimental	letermovir	Drug	Tablet	240 mg	Age/ weight based	Oral	QD from Day 1 through week 14 (~100 days) post-transplant	Test Product	IMP	Sponsor
2	Experimental	letermovir	Drug	Capsule (oral granules)[a]	120 mg	Age/ Weight based	Oral	QD from Day 1 through week 14 (~100 days) post-transplant	Test Product	IMP	Sponsor
3	Experimental	letermovir	Drug	Capsule (oral granules)[a]	30 mg	Age/ Weight based	Oral	QD from Day 1 through week 14 (~100 days) post-transplant	Test Product	IMP	Sponsor
4	Experimental	letermovir	Drug	Capsule (oral granules)[a]	10 mg	Age/ Weight based	Oral	QD from Day 1 through week 14 (~100 days) post transplant	Test Product	IMP	Sponsor
5	Experimental	letermovir	Drug	Intravenous	20 mg/mL vial	Age/ Weight based	Intravenous	QD from Day 1 through week 14 (~100 days) post transplant[b]	Test Product	IMP	Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational medicinal product/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

[a] The oral granules may be administered either by mouth or via G tube/NG tube, provided the participant does not have a condition that may interfere with the absorption of oral formulation (eg, vomiting, diarrhea, or a malabsorptive condition).

[b] Use of IV formulation should generally be limited to 4 weeks or less in duration. The IV formulation should be switched to oral study intervention (ie, at the next planned visit) as soon as such participants are able to swallow and/or the condition necessitating the use of IV formulation resolves.

Dosing of Oral Formulation:

For Age Group 1: Either the currently marketed oral 240-mg tablets (or multiples thereof) for adults will be used (preferably) or, the oral granules will be used for participants unable or unwilling to swallow the adult tablets. The adult tablets may be taken with or without food.

For Age Groups 2 and 3: The only oral formulation that will be used in these groups will be oral granules.

Oral Granule Administration:

Oral granules are encapsulated and may be administered either by mouth using a soft food vehicle, or as a suspension using a G tube/NG tube. Please see Pharmacy Manual for further details on preparation and administration of oral granules.

Table 10 Dosing for Oral Formulations of LET

Age Group	Age Range	BW limits (kg)	Oral dose LET (mg)	Clinical supplies for oral dose [a, c]	Oral dose LET (mg) with CsA	Clinical supplies for oral dose with CsA
1	12 to <18 years	Any weight	480	2x240 mg tablets OR 4x120 mg capsules [b]	240	1x240 mg tablet OR 2x120 mg capsules [b]
2	2 to <12 years	≥30	480	4x120 mg capsules	240	2x120 mg capsules
		18 to <30	240	2x120 mg capsules	120	1x120 mg capsule
		10 to <18	120	1x120 mg capsule	60	2x30 mg capsules
3	Birth to <2 years	10 to ≤15	120	1x120 mg capsule	60	2x30 mg capsules
		7.5 to <10	120	1x120 mg capsules or 4x30 mg capsules	60	2x30 mg capsules
		5.0 to <7.5	60	2x30 mg capsules	40	4x10 mg capsules
		2.5 to <5.0	40	4x10 mg capsules	20	1x10 mg capsule

BW=body weight recorded at enrollment (Day 1) will be used to determine initial dosing. Dose may be adjusted according to the most recent body weight taken per the SoA; CsA=cyclosporin A; LET=letermovir.

[a] Capsules refer to the capsules containing oral granules for administration with soft food or via G tube/NG tube.

[b] For participants unable to swallow tablets.

[c] Alternate combinations may be used to achieve doses, if necessary. These alternate combinations will be communicated separately to investigators.

Dosing of IV Formulation:

For study participants who cannot swallow and/or have a condition that may interfere with the absorption of an oral formulation (eg, vomiting, diarrhea, or a malabsorptive condition), study intervention can be initiated with or switched to the IV formulation (Table 11). The IV formulation should be administered over a period of 60 minutes. A sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials must be used. Use of the IV formulation should generally be limited to 4 weeks or less in duration. However, it will be left to the investigator's discretion to continue IV administration beyond 4 weeks.

Administration of IV Formulation:

Please see Pharmacy Manual for details on preparation and administration of the IV formulation.

Table 11 Dosing for Intravenous Formulation LET

Age Group	Age Range	BW limits (kg)	IV dose LET[a] (mg)	IV dose LET (mg) with CsA[a]
1	12 to <18 years	Any weight	480	240
2	2 to <12 years	≥30	240[b]	240
		18 to <30	120[b]	120
		10 to <18	60[b]	60
3	Birth to <2 years	10 to ≤15	60[b]	60
		7.5 to <10	60[c]	60[b,c]
		5.0 to <7.5	40[c]	40[b,c]
		2.5 to <5.0	20[c]	20[b,c]

BW=body weight recorded at enrollment (Day 1) will be used to determine initial dosing. Dose may be adjusted according to the most recent body weight taken per the SoA; CsA=cyclosporin A; LET=letermovir.

[a] IV formulation concentrate to be diluted per the Pharmacy Manual.

[b] Based on modeling for Age Groups 2 and 3, the IV dose of LET is reduced by 50% compared with oral LET in order to maintain target exposures and no further reduction of IV LET is necessary when coadministered with CsA.

[c] Based on interim analysis results for Age Group 3, dose increase for BW limits <10 kg.

As additional PK analyses are performed during the study, the dose proposed for participants will be confirmed or modified. Recommendations for dose modifications will be communicated to investigators and sites via a PCL.

All supplies indicated in Table 9 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number .

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed in order to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

Participants in this study will be stratified by age group (birth to <2 years, 2 to <12 years, and 12 to <18 years).

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol specified treatment plan for >7 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

It is important for investigators to review each medication (prescription and nonprescription) the participant is taking before starting the study and at each study visit.

- At each visit, participants should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.

Given that the lists below are not comprehensive, the investigator should use his/her medical judgment when a participant presents with a medication not on the list and consult with the Sponsor when appropriate.

6.5.1 Allowed Medications/Therapies

6.5.1.1 Allowed Medications/Therapies That Can be Administered Without Monitoring

The following medications/therapies are allowed in this study without monitoring.

- Standard antimicrobial prophylaxis (eg, levofloxacin for bacteria, fluconazole/ posaconazole for fungi; see Section 6.5.1.2 for recommendations on voriconazole use when coadministered with LET)
- acyclovir, or valacyclovir, for prophylaxis of herpes simplex virus (HSV) or varicella zoster virus (VZV) infections at doses no greater than prohibited doses of these medications (Appendix 10)
- All types of prior conditioning regimens (including myeloablative, reduced-intensity, or nonmyeloablative regimens)

- Prior/Ongoing graft manipulation regimens (including various *ex-vivo* or *in vivo* T-cell depletion or selection regimens)

- GVHD prophylaxis regimens, other than those outlined below in Section 6.5.1.2.

6.5.1.2 Allowed Medications/Therapies to be Administered with Clinical and/or Drug-level Monitoring

The following medications/therapies are allowed when coadministered with LET, but should be used with clinical monitoring for adverse events related to these agents and/or drug-level monitoring of these agents.

When using an allowed concomitant medication please refer to the pediatric prescribing information of each local product circular. Note that all allowed medications in this section have pediatric prescribing information, but not all these agents have prescribing information covering the wide age range of participants (from birth to <18 years of age) that will be evaluated in this protocol.

Note: Since the DDIs may be different when LET is coadministered with CsA, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor, please refer to Section 6.5.2.2 for additional recommendations when LET is coadministered with CsA.

- **CYP3A substrates:**

  - Coadministration of LET with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of coadministered CYP3A substrates (examples: alfentanil, fentanyl, and midazolam). Therefore, frequent monitoring for adverse reactions related to these agents is recommended during coadministration.

  - Dose adjustment of CYP3A substrates with narrow therapeutic range (NTR) may be needed when coadministered with LET (a moderate CYP3A inhibitor). Please consult current prescribing information for monitoring and dosing these products with moderate inhibitors of CYP3A.

    - Cyclosporin A (CsA): Coadministration of LET with CsA increases CsA concentrations. Frequent monitoring of CsA whole blood concentrations should be performed during and at discontinuation of LET and the dose of CsA adjusted accordingly.

    - Sirolimus: Coadministration of LET with sirolimus increases concentrations of sirolimus. Frequent monitoring of sirolimus whole blood concentrations should be performed during and at discontinuation of LET and the dose of sirolimus adjusted accordingly. When LET is coadministered with CsA, refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with CsA.

- Tacrolimus: Coadministration of LET with tacrolimus increases tacrolimus concentrations. Frequent monitoring of tacrolimus whole blood concentrations should be performed during and at discontinuation of LET and the dose of tacrolimus adjusted accordingly.

- Everolimus: Coadministration of LET with everolimus may increase everolimus concentrations. Frequent monitoring of everolimus blood concentrations should be performed during and at discontinuation of LET and the dose of everolimus adjusted accordingly. (**Note:** Please see Section 6.5.2.2 for recommendations for everolimus when LET is coadministered with CsA).

Note: LET dose adjustment is not necessary when coadministered with tacrolimus, sirolimus, everolimus or mycophenolate mofetil.

- **Certain HMG-CoA reductase inhibitors (also referred to as Statins) as substrates of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) and/or CYP3A:**

  - Atorvastatin: The dose of atorvastatin should not exceed a daily dose of 20 mg. (Note: Please see Section 6.5.2.2 for recommendations for the administration of atorvastatin when LET is coadministered with CsA).

  - Fluvastatin, rosuvastatin, lovastatin, or pravastatin: The dose of fluvastatin, lovastatin, or pravastatin may need to be adjusted when coadministered with LET. Monitoring for statin-associated adverse reactions (eg, myalgias, rhabdomyolysis) is recommended during coadministration with LET.

- **Substrates of CYP2C9 and CYP2C19:**

  - Voriconazole: Coadministration of LET with voriconazole decreases the plasma concentrations of voriconazole likely due to induction of CYP2C9 and/or 2C19. If concomitant administration is necessary, close monitoring for reduced effectiveness of voriconazole is recommended.

  - Warfarin: LET may decrease the plasma concentrations of CYP2C9 and/or CYP2C19 substrates (eg, warfarin). Frequent monitoring of international normalized ratio (INR) should be performed while warfarin is coadministered with LET.

  - Proton Pump Inhibitors, such as omeprazole and pantoprazole: LET may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.

6.5.2 Prohibited Medications

Medications/therapies that are prohibited during coadministration with study therapy during the time periods specified are outlined in Section 6.5.2.1. Since the DDI on coadministered drugs may be different when LET is coadministered with CsA than when drugs are

coadministered with LET without CsA, additional prohibited medications when LET is coadministered with CsA are outlined in Section 6.5.2.2.

Letermovir should be administered in a manner consistent with the LET local product circular, including the complete list of prohibited medications (ie, those that are contraindicated or not recommended) in the circular. The local product circular for LET supersedes this section when the product circular is more restrictive. **While the participant is enrolled in the study, only LET provided by the Sponsor as study medication can be administered to the participant.**

If there is a clinical indication for one of these or other medications specifically prohibited during the study, discontinuation from LET may be required. **The investigator should discuss any questions regarding this with the Clinical Director.** The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on LET requires the mutual agreement of the investigator, the Sponsor, and the participant.

6.5.2.1 Medications Prohibited with LET

A. Prohibited Anti-CMV Medications

The following antiviral drugs or therapies for prevention/treatment of CMV are prohibited through Week 24 post-transplant unless required for the initiation of PET or treatment of CMV disease at a CMVi visit:

- Ganciclovir or valganciclovir
- Foscarnet
- Cidofovir

Note: these agents may be used for other indications while participants are on study therapy (eg, foscarnet for the treatment of human herpes virus 6 [HHV-6]).

B. Other Prohibited Agents With Anti-CMV Activity

The following antiviral drugs or therapies for prevention/treatment of CMV are prohibited through Week 24 post-transplant:

- Acyclovir, valacyclovir (at doses greater than those recommended for HSV/VZV prophylaxis: see Appendix 10), famciclovir, or letermovir (not provided by the Sponsor as study medication).
- CMV hyper-immune globulin or intravenous immune globulin.
- Any investigational CMV antiviral agent/biologic therapy, including CMV vaccines.

Note: these agents may be used for other indications while participants are on study therapy (eg, acyclovir for treatment of disseminated zoster).

C. Other Medications Prohibited With LET

The following medications/therapies are prohibited during treatment with study medication and through 28 days following the last dose of study medication:

- Investigational Agents: Unapproved investigational agents or investigational regimens involving combinations of *approved* agents are not permitted except
    - Investigational chemotherapy regimens involving *approved* agents and investigational antimicrobial regimens involving *approved* antibacterial/antifungal/antiviral agents, investigational radiotherapy studies, or other observational studies are allowed.
    - Investigational vaccines (ie, those not licensed or approved for emergency use) are not allowed.

    Note: any licensed COVID-19 vaccine (including for emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
- Herbal Supplements: Herbal supplements are not permitted.
- CYP3A substrates with NTR that can lead to SAEs, including but not limited to:
    - pimozide: Concomitant administration of LET may result in increased concentrations of pimozide due to inhibition of CYP3A by LET, which may lead to QT prolongation and torsade de pointes.
    - ergot alkaloids: Concomitant administration of LET may result in increased concentration of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by LET, which may lead to ergotism.
- Certain Statins (Note: See Section 6.5.2.2 for additional statins that are prohibited for use when LET is coadministered with CsA):
    - simvastatin and pitavastatin.
    - Fixed-dose combinations of statins.
    - Rifampin and other strong inducers (such as phenytoin, carbamazepine, St John's wort [*Hypericum perforatum*], rifabutin and phenobarbital) and moderate inducers such as nafcillin, thioridazine, modafinil, and bosentan.

6.5.2.2 Additional Medications Prohibited when LET is Coadministered with CsA

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on coadministered drugs may be different when LET is coadministered with CsA. Medications listed in this

section pertain to coadministration with LET *with* CsA. In addition to the prohibited medications listed above in Section 6.5.2.1, medications listed in this section are additional medications that are prohibited when coadministered with LET and CsA.

When used together, they should be administered in a manner consistent with the local product circulars (for CsA and if available, for LET), including the complete list of prohibited medications including those that are contraindicated or not recommended. For example, the SmPC for LET has additional contraindications when LET and CsA are administered; the local product circular for LET supersedes this section when the product circular is more restrictive.

- Certain statins: When LET is coadministered with CsA, the magnitude of the increase in statin plasma concentrations is expected to be greater than with LET alone.
    - atorvastatin and lovastatin (**Note:** please see Section 6.5.2.1 for additional prohibited statins when coadministered with LET alone).
- everolimus (**Note:** please see Section 6.5.1.2 for recommendation for everolimus when coadministered with LET alone).
- repaglinide

6.5.3 Rescue Medications and Supportive Care

In the event of CS-CMVi (CMV disease or initiation of PET based on CMV viremia and the clinical condition of the participant [see Section 4.2.1.3]) at any time during the 14-week post-transplant period, study intervention will be discontinued, and the participant may be treated according to the local standard of care (outside the context of the study). In this setting, any of the prohibited anti-CMV medications (outlined in Section 6.5) may be used.

6.6 Dose Modification (Escalation/Titration/Other)

See Section 4.3.1 for the LET dose to be used with or without coadministered CsA.

If CsA is initiated after starting study intervention, the next dose of LET (administered up to 24 hours later) should be decreased as applicable. If CsA is discontinued permanently or for the long term in a participant already receiving LET, the next dose of LET (administered up to 24 hours later) should be increased as applicable. If CsA is temporarily withheld due to high levels detected by therapeutic blood monitoring, the dose of LET need not be adjusted.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.4.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10.

A participant **must be** discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive pregnancy test.
- The participant develops CS-CMVi as determined by the investigator (Section 4.2.1.3).
- The participant develops (one or more of the following):
    - An elevated AST or ALT lab value that is ≥3 × ULN and an elevated total bilirubin lab value that is ≥2 × ULN and, at the same time, an alkaline

phosphatase lab value that is <2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing

- Both moderate hepatic insufficiency (Child-Pugh Class B; Appendix 9) and moderate-to-severe renal insufficiency (defined as creatinine clearance <50 mL/min as calculated by the Cockcroft-Gault equation (for Age Group 1) or <50 mL/min per 1.73 m^2 as calculated using the modified Schwartz equation (for Age Group 2); Participants in Age Group 3 should be discontinued if they have moderate hepatic insufficiency and creatinine clearance <20 mL/min per 1.73 m^2 calculated using the modified Schwartz equation; see Appendix 12 for Cockcroft-Gault and modified Schwartz equations.
- Severe hepatic insufficiency (Child-Pugh Class C; Appendix 9).
- Either
  a) a need for renal replacement therapy (eg, hemodialysis, peritoneal dialysis)

  OR

  b) has end-stage renal impairment with creatinine clearance ≤10 mL/min as calculated by the Cockcroft-Gault equation (for participants ≥12 years of age) or ≤10 mL/min per 1.73 m^2 as calculated using the modified Schwartz equation (for participants <12 years of age; Appendix 12).

- **For Age Group 3 participants only,** the IV formulation of LET should be discontinued when the creatinine clearance (as determined by the using the modified Schwartz equation) meets the following criteria:
  - decreases by ≥50% from the baseline value (ie, on the day IV LET was initiated)

  AND

  - is below the lower bound of normal creatinine clearance for the age at the time of assessment (Table 12).

- Note: The decrease in creatinine clearance should be confirmed by repeat testing as soon as possible. The confirmatory sample should be obtained no later than 4 days following the report of the first test result. If confirmed, the IV formulation should be discontinued.

Table 12 Lower Bound of Creatinine Clearance by Age

Age at time of assessment	Lower bound of normal creatinine clearance[a, b]
18 months to <2 years	≥76 mL/min/1.73m^2
12 to <18 months	≥73 mL/min/1.73m^2
8 to <12 months	≥65 mL/min/1.73m^2
14 weeks to<8 months	≥57 mL/min/1.73m^2
6 to <14 weeks	≥47 mL/min/1.73m^2
2 to <6 weeks	≥41 mL/min/1.73m^2
1 to <2 weeks	≥35 mL/min/1.73m^2
Birth to <1 week	≥20 mL/min/1.73m^2

[a] Modified Schwartz equation used to calculate creatinine clearance (Appendix 12.1).

[b] Lower bound of normal creatine clearance taken from published lower bound standard deviation of age-appropriate means (Biron, Schwartz).

[Brion, L. P., et al 1986] [Schwartz, G. J. 2009]

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will vary; see Appendix 2.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent, and assent if applicable, from each potential participant or their legally acceptable representative prior to participating in this clinical study or FBR . If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on a consent/assent form. The form must include the trial protocol number, trial protocol title, dated signature, and /agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent/assent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial informed consent/assent form, any subsequent revised consent/assent, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or their legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

The assent, as applicable, will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent/assent to the participant, or the participants legally acceptable representative, answer all of his/her questions, and obtain documented informed consent/assent before performing any procedure related to FBR. A copy of the informed consent/assent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification

card immediately after the participant provides documented informed consent/assent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at screening.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement. Prior medication taken by the participant within 30 days prior to enrollment will be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

All concomitant medications should be reviewed and documented while participants are on study intervention.

Anti-CMV medications administered for treatment of CMV disease or for initiation of PET, medications used for HSV/VZV prophylaxis, and all drug/biologic therapies used to prevent/treat GVHD should be recorded at every visit through Week 48 post-transplant.

During the follow-up period (after Week 14 post-transplant through Week 48 post-transplant or from the time the participant stops taking the study intervention through Week 48 post-transplant), concomitant medication review is **limited to** the above and all antimicrobials (antibacterials, antifungals, antiparasitic agents and antivirals), chemotherapy agents, and immunosuppressant agents.

8.1.6 HSCT Details Review

All relevant data about the HSCT will be collected on Day 1 (enrollment). This includes details regarding the conditioning regimen used, the date and type of transplant, primary reason for transplant, the source of stem cells, type of graft manipulation, presence of GVHD, and GVHD prophylaxis regimen (if any) used.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Those participants who meet laboratory exclusion criteria may have the testing repeated one time as described in Section 5.2. Only the exclusionary lab is to be retested. Any individual who has more than one screening will retain the original screening number assigned at the original screening visit.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.9 Study Intervention Administration

The first dose of study intervention will be administered at the study site on Day 1 after enrollment/allocation. A sample for CMV DNA PCR must be collected prior to initiating study intervention.

The oral granules may be administered by mouth (with a soft food vehicle), or via a G tube/NG tube. Refer to Pharmacy Manual for further details on preparation and administration of oral granules.

For IV formulation, the study pharmacist (or appropriately qualified designee) will be responsible solely for the preparation of the IV study intervention. The IV formulation will be administered by site personnel through a sterile 0.2-micron or 0.22-micron PES in-line filter and using DEHP-free IV bags and infusion set materials. Refer to the Pharmacy Manual for further details on preparation and administration of the IV formulation.

Please refer to Section 6.1 for details regarding administration of oral granules.

8.1.9.1 Timing of Dose Administration

Study intervention should be taken at approximately the same time each day for the duration of the treatment period of the study (once daily for LET). Treatment compliance is further described in Section 6.4.

If a participant misses a dose of LET, the missed dose should be taken as soon as possible during the same day. Then, the next dose should be taken at the normally scheduled time. However, if more than 12 hours have elapsed after the regular dosing time, then the missed

dose should be skipped, and the normal dosing schedule should be resumed. The next dose should not be doubled in order to "make up" what has been missed.

If a participant vomits within 2 hours of an administration of tablets or oral granules, the full dose can be repeated one time within 6 hours of vomiting. If a participant vomits and it has been longer than 2 hours from the time of an administration of tablets or oral granules, the dose should not be repeated. Instead, the next dose should be taken at the usual time the following day.

8.1.9.2 Study Medication Diary

For hospitalized participants receiving either LET oral tablets or granules, study intervention will be recorded in the participant's chart; this will serve as the source document. For participants receiving oral tablets or granules outside of the hospital setting (ie, receiving oral LET at home), study intervention will be recorded in a paper study medication diary (SMD).

The investigator/study coordinator will review and provide instructions to the participant/legally acceptable representative on the use of the SMD, which is to be completed during the treatment period of the study. The investigator/study coordinator will be responsible for entering the participant's identification (randomization/allocation number), visit weeks, the diary distribution date, and the information to indicate the appropriate dosage form and quantity before giving the SMD to the participant/legally acceptable representative.

The participant/legally acceptable representative will be instructed on proper storage, preparation and administration of LET oral granules and to use the SMD to record dates/times and the number of tablets/capsules of LET dosed for the entire treatment period; participants on oral granule formulation given by mouth will also record soft food information, whether the entire dose was consumed and the timeframe over which the dose was consumed. Participants on oral granules administered via G tube/NG tube will record whether the entire dose was given. In addition, the reason for any missed or incorrect doses or entire dose not being consumed/given will need to be recorded. Only the participant/legally acceptable representative should enter information into the SMD. The participant/legally acceptable representative is to return the completed SMD at each scheduled visit.

For all visits during the treatment period, site personnel are required to verify the accuracy of the dosing recorded in the SMD by comparing entries with amounts of unused study medication. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the participant, and the explanation must be documented. The investigator/study coordinator will be responsible for transferring the appropriate information from the SMD to the appropriate CRF.

Training participants/legally acceptable representative on administration of oral granules

For participants discharged on oral granules to be administered either by mouth or via G tube/NG tube on an outpatient basis, site personnel must provide training to the

participant/legally acceptable representative on preparation and administration of the oral granules prior to discharge, preferably during the preceding week (refer to the Pharmacy Manual on detailed instructions; instructions are also briefly provided in the SMD). Such training also should be provided when the route of administration of oral granules changes (eg, from G tube/NG tube to administration by mouth). Documentation of such training and that the participant/caregiver has understood the instructions and will be able to take the oral granules correctly must be entered in the participant's chart, which will serve as the source document.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Early Study Discontinuation Visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

8.1.10.1 Withdrawal From Future Biomedical Research

A Participant's consent for Future Biomedical Research may be withdrawn by the participant or the participant's legally acceptable representative (as appropriate). A participant's consent may be withdrawn at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.12 Domiciling

For participants who will undergo intensive PK sampling, the investigator should make arrangements (including local accommodations outside the context of hospitalization, if needed/warranted) such that all PK sampling at specified time points can be performed as scheduled.

8.1.13 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 CMV DNA PCR Testing

CMV DNA PCR testing will be performed using a qualitative or quantitative CMV DNA PCR assay at the local laboratory. The same PCR assay method should be used for testing throughout the study for each individual participant. When available, quantitative CMV DNA PCR is preferable over qualitative testing. After the initial screening visit until enrollment, samples must be collected and tested once per week. The test should be repeated one more time within 5 days of the planned enrollment date to ensure the result is still negative. Thereafter, samples will be collected as indicated in the SoA (Section 1.3). CMV DNA PCR testing may be conducted within 3 days prior to a scheduled study visit and no later than the day of the scheduled study visit. (This CMV DNA PCR testing window is not applicable to a CMV Infection Visit).

For participants who develop CS-CMVi (through 24 weeks post-transplant): When the investigator intends to initiate either treatment for CMV disease or PET, the participant should have a CMV Infection Visit. It is very important to ensure that all procedures, as outlined in the SoA (Section 1.3), are performed at the CMV Infection Visit **immediately prior to** the initiation of treatment of CMV diseases or initiation of PET (ie, on the same day anti-CMV therapy or PET is initiated). Thereafter, the participant should be discontinued from LET (if applicable) and treated according to the local standard of care (outside the context of the study). Such participants will continue to be followed in the study (despite discontinuing study intervention and initiating anti-CMV therapy) and complete all remaining study visits (including all subsequent treatment period visits). At such subsequent visits, all procedures specified in the SoA (Section 1.3) should be completed with the exception of study intervention administration, PK assessments and palatability assessments.

Additional CMVi Visit(s) are also required for every new episode of CS-CMVi following the initial episode through Week 24 post-transplant.

Note on re-initiation of study intervention: There may be instances when lab test results for CMV DNA PCR obtained on the day of PET initiation may be negative (CMV DNA undetectable) and the investigator may wish to discontinue PET. The decision to stop PET in the event of a negative (CMV DNA undetectable) result collected on the day of PET initiation resides with the investigator caring for the participant. Therefore, in the event the CMV DNA sample at PET initiation is negative for CMV viremia, the Sponsor will allow for LET to be restarted at the investigator's discretion, once PET is discontinued. In such instances, study intervention should be restarted within 7 days from the date on which study intervention was stopped. It is important to note that the status of the participants' study intervention in IRT should NOT be changed until the investigator is certain that LET prophylaxis will be permanently discontinued.

Assessment of CMV Disease

CMV disease will be assessed at every visit from screening through Week 24 post-transplant. Diagnostic criteria for the evaluation of CMV disease are outlined in Appendix 8. If CMV Disease is suspected, site should perform the CMV Infection Visit instead of the scheduled visit assessments (Section 1.3). The investigator will ensure that clinical information, radiology results, and specimens for the appropriate diagnostic tests (including, but not limited to, viral culture, histopathology, immunohistochemical analysis, in situ hybridization, CMV DNA PCR) as outlined in Appendix 8 will be collected. Both "probable" or "proven" cases of CMV disease should be reported.

8.2.2 CMV DNA Sequence Analysis

Sample collection, storage, and shipment instructions for plasma samples will be provided in the central laboratory manual.

CMV DNA sequence analysis will be performed on samples from participants who meet the criteria for CS-CMVi at the CMV infection visit. Resistance to LET will be assessed by genotypic analysis of the CMV terminase complex genes (UL56, UL89, and UL51) in DNA extracted from plasma samples collected as indicated in the SoA (Section 1.3) with detectable CMV viral DNA. Samples will be analyzed by next generation sequencing technology through an established contract laboratory with validated protocols in place. In participants with multiple CMV-positive samples, the last on-therapy and/or follow-up samples will be used for analysis.

Because plasma volume collection is limited in the pediatric population compared with adults, actual sample volume collected may be less than expected. If insufficient plasma is available for resistance genotyping of all 3 CMV terminase complex genes, testing of the UL56 gene will be prioritized. In vitro studies have confirmed that substitutions in the UL56 protein are both necessary and sufficient for LET resistance. Mutations in the UL89 and UL51 genes alone have little impact on LET activity, but further decrease LET potency in combination with UL56 mutations in vitro. Therefore, UL56 gene sequencing will be prioritized for participants receiving LET who meet the criteria for CS-CMVi. UL89 and UL51 sequencing will also be attempted, provided sufficient plasma is available.

Phenotypic analysis may be performed on any UL56, UL89, or UL51 DNA sequences, which encode amino acid substitutions that have not been previously characterized via phenotypic analysis.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study for research testing, including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 2.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at visits specified in the SoA (Section 1.3). The complete physical examination includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated.

A brief directed physical examination may be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at any other visit when clinically indicated.

Height and weight will be measured and recorded per the SoA. Weight will be used to guide LET dosing. **Body weight recorded at enrollment (Day 1) will be used to determine the initial dosing. Dose may be adjusted according to the most recent body weight taken per the SoA.** Height and weight will be measured per SoA to monitor creatinine clearance, as calculated by the Cockcroft-Gault equation (for participants ≥12 years of age) or by the modified Schwartz equation (for participants <12 years of age) using serum creatinine (Appendix 12).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be assessed as indicated in the SoA (Section 1.3).

Vital signs will include heart rate, blood pressure, respiratory rate, and body temperature (oral). Participants should be resting for at least 5 minutes prior to measurement of vital signs.

Note: Temperatures should be taken orally, but if oral is not possible, tympanic, rectal, and axillary temperatures are acceptable.

Vital signs will be measured after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

8.3.3 Electrocardiograms

Single 12-lead electrocardiogram (ECG) will be obtained and reviewed locally by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Participants should be shaved (if necessary) for proper lead placement. Participants should be resting for at least 5 minutes prior to having ECG readings obtained.

8.3.4 Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 Date of Menarche

The date of menarche must be recorded for females who have previously experienced menarche. Once a date of menarche has been confirmed, the participant is considered to be a woman of child bearing potential (WOCBP). For prepubescent females, site staff should continue to review and record, as appropriate, at each visit during the treatment period.

8.3.6 Confirmation of Contraception (WOCBP Only)

Throughout the screening and treatment periods, precaution must be taken to avoid pregnancy in WOCBP. Confirmation must be obtained and documented by site personnel that WOCBP are using acceptable methods of contraception (Appendix 5). This assessment must be documented in the participant's study chart at each specified visit.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE, as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3. Investigators need to document if an AE and/or SAE was associated with a medication error, misuse, or abuse.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization must be reported by the investigator if the participant dies, is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 28 days following cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Thereafter, only SAEs related to study medication or SAEs leading to death will be collected through Week 48 post-transplant.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a

death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated Table 13.

Table 13 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-Specified Follow-up Period (28 days following last dose of study medication)	**Reporting Time Period:** After the Protocol-Specified Follow-up Period (from 28 days following last dose of study medication through Week 48 post-transplant)	**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - death due to any cause - due to protocol-specified intervention - causes exclusion	Report all	Report only if: - drug related. OR -SAEs leading to death, regardless of causality	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (ECI) (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-Specified Follow-up Period (28 days following last dose of study medication)	**Reporting Time Period:** After the Protocol-Specified Follow-up Period (from 28 days following last dose of study medication through Week 48 post-transplant)	**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not Applicable.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- Potential DILI events defined as an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than 2 times the prescribed dose specified in Section 6.6 (Dose Modification [Escalation/Titration/Other]).

Sponsor does not recommend specific treatment for an overdose. Overdose during the study will be a reportable safety event (see Section 8.4.1 and Appendix 3 for further details).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Plasma samples for sparse PK will be collected in all participants.

Plasma samples for intensive PK (oral formulation) will be collected from all participants in Panel A of Age Groups 1 and 2 who receive oral LET formulation (by mouth or G tube/NG tube) from Day 1 until Day 7 visit. Additionally, plasma samples for intensive PK (IV formulation) will be collected for any study participant who receives at least 5 consecutive days of IV dosing and has not had prior intensive PK collected on the oral formulation. The proposed PK sampling scheme for sparse PK and intensive PK across all age groups is provided in Table 14.

8.6.1 Blood Collection for Letermovir Pharmacokinetic Sampling

Sample collection, storage, and shipment instructions for PK samples will be provided in the laboratory manual. PK samples should not be collected in participants after discontinuation of study intervention.

On all PK visits where a predose sample will be collected, the visit should occur prior to the participant's regular time for taking their study intervention and the participant should withhold their dose until after the predose sample is drawn. If it is not feasible to schedule the visit prior to the participant's regular time for taking their study intervention, the participant should withhold their dose until reporting to the clinic. The predose PK sample will be obtained and the next scheduled dose will then be administered at the clinic. The date and time of each PK sample as well as the date and time of the last dose of study medication prior to the PK sample will be recorded.

For participants receiving oral granules in soft food, the soft food vehicle used to administer the last dose of study medication prior to the PK sample as well as the day of the PK sample will also be recorded. For participants receiving oral granules via G tube or NG tube, the use of these tubes will be recorded.

If a participant vomits following administration of oral LET while intensive PK sampling is ongoing, no further samples should be collected, and the Sponsor should be informed to determine further course of action.

Table 14 Pharmacokinetic Sampling for Protocol 030

PK Type	LET Route of Administration	Study Visit	PK Sample Times[a]	Primary PK Parameters	Other PK Parameters
Intensive PK for LET	Oral Formulations[b]	Day 7[c] (Days 7-9)	Predose (0 to 20 min before dose) 1 h (± 10 min) 2.5 h (± 30 min) 8 h (± 2 h) 24 h (0 to 2 h before next dose)	AUC0-24h Cmax Ctrough	Tmax t1/2 CL/F Vd/F
	IV[d]	Any	Predose (0 to 20 min before IV infusion begins) 1 h (0 to 10 min after IV infusion ends) 2.5 h (± 30 min) 8 h (± 2 h) 24 h (0 to 2 h before next dose)	AUC0-24h Ceoi Ctrough	t1/2 CL Vd
Sparse PK for LET	Oral Formulations[b]	Weeks 2, 4, 6, 8, 10, 12, 14, CMVi[e] or Early Discon[e] Visits	Predose (0 to 2 h before dose)	Ctrough	
	IV	Weeks 2, 4, 6, 8, 10, 12, 14	Predose (0 to 2 h before IV infusion begins)	Ctrough	
HPCD PK sampling	IV	See note[f]	1 h after initiating the IV infusion (within 10 mins of ending a 60 min IV infusion) on the 4th consecutive day of IV infusion 24 h after initiating the IV infusion (0 to 2 hours before the next dosing) on the 5th consecutive day of IV LET administration	PK exploratory parameters	IV

PK Type	LET Route of Administration	Study Visit	PK Sample Times[a]	Primary PK Parameters	Other PK Parameters

AUC0-24h=area under the concentration-time curve from time 0 to 24 hours; CEIO=concentration at the end of infusion; CL= clearance; Cmax=maximum concentration; CMVi=cytomegalovirus infection; Ctrough= trough concentration; Discon=discontinuation; F=bioavailability; h=hour(s); HPCD=hydroxypropyl-beta-cyclodextrin; IV=intravenous; LET=letermovir: min=minute; min(s)=minute(s); PK=pharmacokinetics; t1/2=apparent half-life; Tmax=time to maximum concentration; Vd=apparent volume of distribution.

[a] Sample collection times for IV formulation are relative to start of IV infusion, with acceptable ranges noted.

[b] The oral formulations may be tablets or oral granules. Oral granules may be administered either by mouth or via G tube/NG tube, provided the participant does not have a condition that may interfere with the absorption of oral formulation (eg, vomiting, diarrhea, or a malabsorptive condition).

[c] All participants in Panel A of Age Groups 1 and 2 who receive oral formulation of LET from Day 1 until Day 7 visit will have intensive PK on Day 7. All participants in Age Group 3 will have intensive PK sampling done regardless of the formulation received (starting on either the fifth day of IV LET or the seventh consecutive day of oral LET, whichever comes first).

[d] Intensive PK on IV formulation will be collected from participants who have NOT had intensive PK on the oral formulations (oral granules/oral tablet); sample collection will start on the 5th consecutive day of IV dosing.

[e] Collected only if the participant is still on LET at the CMVi or Early Discontinuation Visit and the visit occurs on or before Week 14.

[f] Start on the 4th consecutive day of IV dosing for participants in Age Group 3.

8.6.2 Blood Collection for HPCD Pharmacokinetic Sampling

Whole blood will be collected from Age Group 3 participants starting **on the fourth consecutive day** of IV LET administration, as follows:

- The first sample on that day will be taken 1 hour after initiating the IV infusion (within 10 minutes of ending the 60 minute infusion).
- The second sample must be taken 24 hours after initiating the IV infusion (0 to 2 hours before the next dosing) on the fifth consecutive day of IV LET administration.

The central laboratory manual contains instruction for sample handling and processing.

All Age Group 3 participants, for whom HPCD sampling is collected, will also need local laboratory testing for serum creatinine levels to correlate any changes in creatinine clearance with HPCD levels as outlined in Section 8.6.2.1.

8.6.2.1 Additional Creatinine Clearance Measurements for Participants in Age Group 3 Receiving Intravenous Letermovir Formulation

Timepoints for collection of HPCD PK and creatinine clearance measurements (which would require local laboratory testing for serum creatinine) depend on the number of consecutive days of IV LET and whether it is the initial or subsequent IV LET dose (Table 15). Creatinine clearance measurements should be repeated every time a subsequent course of IV formulation is initiated.

Table 15 Creatinine Clearance Timepoints for Age Group 3 Participants Receiving Intravenous Letermovir

Course and Duration of IV LET	Collection of HPCD PK Sampling (Yes/No)	Collection of Creatinine for Creatinine Clearance
First course ≥4 days at any time during treatment	Yes	• 1st day of IV LET administration (prior to initiating IV LET) • 0 to 2 hours before the next dose of LET (at the same time as the second HPCD PK sample is collected) • last day of IV LET (immediately after discontinuing the infusion, if IV LET continues beyond 5 consecutive days)
All other course(s) regardless of duration	No	• 1st day of IV LET administration (prior to initiating LET) • last day of IV LET (immediately after discontinuing the IV)
HPCD=hydroxypropyl-beta-cyclodextrin; IV=intravenous; LET=letermovir.		

8.7 Pharmacodynamics

No pharmacodynamic parameters will be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant provides documented informed consent/assent for FBR, the following specimens will be obtained as part of future biomedical research:

- Residual DNA from buccal swab for future research
- Leftover plasma from CMV viral resistance samples stored for future research.

8.9 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for buccal swabs will be provided in the laboratory manual.

8.10 Palatability and Acceptance Assessment

The PAA (Appendix 11) is to be completed for all participants on the first day of oral granule administration and repeated one week later. The PAA should be implemented with the following recommendations:

- **From Birth to Age 4 years**: Completion by an observer (legally acceptable representative/caregiver/health care provider).

- **Ages 5 to 13 years**: Combined completion where the participant completes the faces question, and the observer completes the remaining questions.

- **Ages 14 to less than 18 years**: Completion directly by the participant, preferred when possible.

Observer assessments should be based on what the legally acceptable representative/caregiver/health care provider has observed directly during and after medication administration, including the participant's facial expressions, behavior, and what the participant says. Only individuals who have actually observed the participant taking the medication should complete the assessment.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Screening of potentially eligible participants may begin within 15 days prior to transplantation, but enrollment/allocation must occur no later than 28 days post-transplant. The informed consent and assent (as applicable) must be obtained before any study-specific procedure is performed. Potential participants will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as described in Sections 5.1 and 5.2. All screening procedures listed under Visit 1 of the Study SoA (Section 1.3) will be performed. Laboratory tests including chemistry, hematology, urinalysis, prothrombin time (PT)/coagulation, HIV, and hepatitis B and C tests will be performed locally. As noted in Section 5.2, participants who meet laboratory exclusion criterion 6 or 7, at the discretion of the investigator, may have repeat testing done one time within 5 days prior to enrollment.

Participants who are WOCBP will be instructed that they are required to use birth control as specified in Appendix 5 starting from the time of consent through 28 days after the last dose of study intervention (or longer if dictated by local regulations). Participants will also be instructed about the restrictions for concomitant medications, as noted in Section 6.5.

Presence of CMV disease in the screening period will be assessed according to Appendix 8.

8.11.2 Treatment Period Visits

Study intervention (LET) may begin as early as the day of transplant and no later than 28 days post-transplant. Study intervention will continue through Week 14 (~100 days) post-transplant. Study visits will occur weekly through Week 14 (~100 days) post-transplant. For the purposes of this study, "Treatment Period" refers to the period from Day 1 through Week 14 post-transplant, regardless of when a participant may have discontinued treatment with LET.

The Day 1 Visit (as shown in the SoA, Section 1.3.1) will be day the participant is enrolled/allocated and LET is initiated. Study intervention will continue through the End of Treatment Visit. **The End of Treatment Visit may occur at the Week 10, 11, 12, 13, or 14 Visit depending on when study intervention is started during the 28-day post-transplant window.** For example, if LET is started on the day of transplant, the End of Treatment Visit will be the Week 14 Visit (which corresponds to Week 14 post-transplant). If LET is started 28 days post-transplant, the End of Treatment Visit will be the Week 10 Visit (which corresponds to Week 14 post-transplant).

All procedures listed under the study visits in the SoA (Section 1.3.1) will be performed at the corresponding visit. After allocation, a complete physical examination does not need to be performed at every visit; a targeted physical examination should be performed only when clinically indicated.

8.11.2.1 Day 1 Visit

Day 1 procedures/assessments listed on the SoA (Section 1.3.1) must be performed prior to initiation of study intervention. The weight of the participant on Day 1 will be used to determine LET dose (Section 6.1).

For female participants of childbearing potential, a urine or serum pregnancy test will be performed at the site prior to the initiation of study intervention. If the urine or serum pregnancy test result is negative, the participant will be eligible for allocation and the remainder of the Day 1 testing/procedures will be performed. If the urine or serum pregnancy result is positive, the participant must not be allocated.

8.11.2.2 Study Intervention Administration Visit

Following completion of the Day 1 procedures/assessments and confirmation of eligibility, the participant will be allocated/enrolled. Sites should not allocate the participant for study intervention (LET) administration until the participant has met all eligibility criteria for the study and is ready to receive the first dose of LET on Day 1. The site pharmacist or study coordinator will contact the IRT for assignment to allocate the participant to LET. The dose of LET will be determined by the participant's weight at Day 1, the formulation administered, and by whether the participant is receiving concomitant CsA (see Section 6.1 for specific details of dose selection and administration instructions). **Dose may be adjusted thereafter, according to the most recent body weight taken per the SoA**

Participants in Panel A of Age Groups 1 and 2:

- Must initiate LET using an oral formulation (either tablets or oral granules; oral granules may be administered by mouth or via G tube/NG tube) from the day of enrollment through the completion of the intensive PK sampling at the Day 7 visit.

- May not receive concomitant administration of CsA from the day of enrollment through the completion of the intensive PK sampling at the Day 7 visit.

- These restrictions are not applicable to participants enrolled in Age Group 1 (Panel B only), Age Group 2 (Panel B only), or for participants in Age Group 3; although all participants should preferably be initiated on oral LET formulation. In the event that a participant enrolled in Panel A has a need to either (1) switch to IV formulation administration or (2) to have CsA coadministered prior to the Day 7 visit, they may do so and will be permitted to continue on LET as appropriate. In such an event, the participant will not have intensive PK samples drawn at the Day 7 visit. If a participant switches to IV formulation or has a new requirement for CsA coadministration, the site is required to notify the Sponsor immediately. The Sponsor will make arrangements for an additional participant to be enrolled in the corresponding panel to maintain n=6 PK-evaluable participants.

In the event that participants who were initiated on an oral formulation subsequently develop a condition (eg, vomiting, diarrhea, or a malabsorptive condition) that may interfere with the absorption of the tablets, these participants can be switched to the IV formulation. For participants who are switched to the IV formulation (Panel A or B), or who initiated with the IV formulation (Panel B only), these participants should be switched to oral LET as soon this participant is able to swallow and/or the condition necessitating the use of the IV formulation resolves (ie, at the next planned dose). Use of the IV formulation should generally be limited to 4 weeks or less in duration; however, it will be left to the investigator's discretion to continue IV administration beyond 4 weeks, if the benefit/risk ratio supports continued administration.

LET may be used with or without concomitant CsA. See Section 6.1 for the LET dose to be used with or without coadministered CsA and for details of study drug modification if concomitant CsA is initiated or discontinued.

8.11.2.3 Additional Treatment Period Visits

Procedures/assessments listed on the SoA (Section 1.3.1) must be performed at all the weekly study visits during the treatment period.

Throughout the treatment period precaution must be taken to avoid pregnancy in WOCBP. Confirmation must be obtained and documented by site personnel that WOCBP are using acceptable methods of contraception (Appendix 5). This assessment must be documented in the participant's study chart at each specified visit.

From Day 1, through Week 14 (~100 days) post-transplant participants will be assessed for CMV disease and CMV DNA PCR should be tested at the local laboratory as per the SoA (Section 1.3.1).

8.11.3 Follow-up Period/Visits

As stated in Section 8.11.2, participants will receive study intervention with LET for 14 weeks post-transplant (ie, participants will receive approximately 10 to 14 weeks of LET depending on initiation of study intervention in relation to the date of transplant). After the last day of study intervention, participants will be followed via study visits at the site from

Week 16 to Week 24 post-transplant. These visits will occur every 2 weeks and all procedures listed in the SoA (Section 1.3.2) corresponding to the visits will be performed.

All participants will continue to be assessed for CMV disease through Week 24 post-transplant and CMV DNA PCR should be tested at the local laboratory as per the SoA (Section 1.3).

Subsequent post treatment follow-up visits will occur at Weeks 32, 40, and 48 post-transplant (telephone contact) and all procedures listed in the SoA (Section 1.3.2) corresponding to the visits will be performed.

Adverse event monitoring should include the collection of all adverse events while on study intervention and for 28 days following completion of study intervention in all participants. Thereafter, only drug-related SAEs and SAEs leading to death will be collected through Week 48 post-transplant.

8.11.4 Participants Discontinuing Study Intervention but Continuing to be Monitored in the Study

Participants who discontinue study intervention (LET) for any reason **will continue to be followed in the study** as outlined in the Study SoA (Section 1.3.1), provided informed consent has not been withdrawn.

8.11.4.1 Discontinuation of Study Intervention Due to CS-CMVi

As all participants in the study will receive the study intervention (LET) through Week 14 post-transplant, LET should be discontinued when the CMV infection Visit occurs prior to the End of Treatment Visit. **A sample for CMV DNA PCR should be collected immediately prior to the initiation of PET or treatment of CMV disease**. Such participants **will continue to be followed in the study** (despite discontinuing LET and initiating anti-CMV therapy) and complete all remaining study visits (including all subsequent treatment period visits). All procedures as outlined in the SoA (Section 1.3.1), with the exception of study intervention administration, PK sampling, collection of samples for PT/INR, Child-Pugh score assessments, and study medication diary review, will be performed for the remainder of the study.

8.11.4.2 Discontinuation of Study Intervention for Reasons Other Than CS-CMVi

Participants who discontinue study intervention (LET) prior to the last scheduled treatment visit for reasons other than CS-CMVi (eg, for an AE) **will continue to be followed in the study** and complete all remaining study visits regardless of when cessation of study intervention occurs. All procedures as outlined in the SoA (Section 1.3.1), with the exception of study intervention administration, PK sampling, collection of samples for PT/INR, Child-Pugh score assessments, and study medication diary review, will be performed for the remainder of the study.

8.11.5 Discontinuation from Study

8.11.5.1 Study Discontinuation Prior to Week 24 Post-transplant:

Participants who prematurely discontinue the study (eg, withdrawal of consent) prior to Week 24 post-transplant will have an **Early Study Discontinuation Visit**. It is important to ensure that all procedures, as outlined in the Study SoA (Sections 1.3.1 and 1.3.2), are performed for such participants at this visit prior to discontinuing the participant from the study. A sample for CMV DNA PCR testing should be collected at this visit.

8.11.5.2 Study Discontinuation After Week 24 Post-transplant

All participants who are discontinued from the study after Week 24 post-transplant should have all information collected at the last visit (as outlined in the Study SoA, Section 1.3.2), prior to discontinuing the participant from the study.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Phase 2b open-label, single-arm study to evaluate pharmacokinetics, safety, efficacy and acceptability/palatability of LET in pediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic haematopoietic stem cell transplantation (HSCT).
Treatment Assignment	This will be an open-label, nonrandomized study.
Analysis Populations	Pharmacokinetics: Per Protocol (PP) Safety: All Participants as Treated (APaT) Efficacy: Full Analysis Set (FAS)
Primary Endpoint(s)	AUC0-24, Cmax, (for participants receiving oral formulation), Ceoi, (for participants receiving IV formulation), and Ctrough
Key Secondary Endpoints	**Safety:** Number of participants experiencing • Adverse Events (AEs) • AEs Resulting in Study Medication Discontinuation **Efficacy:** Clinically significant CMV infection (CS-CMVi) through Week 14 post-transplant and through Week 24 post-transplant. **Palatability:** Score on a palatability scale

Statistical Methods for Key Pharmacokinetic/ Efficacy Analyses	AUC0-24, Cmax, and Ctrough will be calculated, and geometric means and 95% confidence intervals (CIs) will be provided for AUC0-24, Cmax, and Ctrough by age group and dose. The proportion of participants with CS-CMVi through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant will be estimated using a 95% CI (via the Clopper-Pearson method). The missing data approach will be Non-Completer= Failure (NC=F) approach.
Statistical Methods for Key Safety Analyses	Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs and ECG parameters. Descriptive statistics will be provided for these safety parameters.
Interim Analyses	An external DMC will be appointed and will review the safety and tolerability data. The DMC will periodically review the safety data at the following time points: 1) when 6 PK-evaluable participants in Age Group 1, Panel A have completed intensive PK sampling. 2) when 6 PK-evaluable participants in Age Group 2, Panel A have completed intensive PK sampling. 3) when ~10 (which is ~50%) of participants in Age Group 1, Panel B have completed the Week 4 visit. 4) when ~10 (which is ~50%) of participants in Age Group 2, Panel B have completed the Week 4 visit. 5) when at least 3 participants in Age Group 3 have completed intensive PK sampling. This will supplement routine in-house medical monitoring.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	**PK**: A sample size of 6 in Age Group 1 and 2 has approximately 95% power to show that the 95% confidence interval of the geometric mean of AUC0-24 in this age group will be within 60% and 140% of the geometric mean estimates of the AUC0-24 of LET. A sample size of 8 in Age Group 3 has approximately 99% power to show that the 95% confidence interval of the geometric mean of AUC0-24 in this age group will be within 60% and 140% of the geometric mean estimates of the AUC0-24 of LET.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. The statistical analyses of the PK data will be conducted in collaboration with the Pharmacokinetics, Pharmacodynamic and Drug Metabolism and Clinical Research departments of the Sponsor.

This study is being conducted as a nonrandomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule for study intervention assignment. Allocation number will be assigned via an IRT.

Planned interim analyses for ongoing safety monitoring are described in Section 9.7.

9.3 Hypotheses/Estimation

There are no hypotheses to be tested in this study. Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Pharmacokinetics, safety, and efficacy endpoints that will be evaluated are listed below.

9.4.1 Pharmacokinetics Endpoints

An initial description of PK endpoints is provided in Section 4.2.1.1. The primary PK endpoints for LET are: AUC0-24, Cmax (for participants receiving oral formulation), Ceoi (for participants receiving IV formulation), and Ctrough. Additional PK parameters for participants receiving oral formulations are time to maximum observed plasma drug concentration (Tmax), half-life (t1/2), apparent clearance (CL/F), and apparent volume of distribution (Vd/F). Additional PK parameters for participants receiving IV formulation are half-life (t1/2), clearance (CL), and volume of distribution (Vd).

9.4.2 Safety Endpoints

An initial description of safety endpoints is provided in Section 4.2.1.2.

All AEs will be collected through 28 days following the last dose of study medication in all participants. Thereafter, only drug-related serious adverse events (SAEs) and SAEs leading to death will be collected through Week 48 post-transplant.

Safety endpoints will be analyzed using a 3-tiered approach (Section 9.6.3).

9.4.3 Efficacy Endpoints

An initial description of efficacy endpoints is provided in Section 4.2.1.3.

The key efficacy endpoints will be the proportion of participants with CS-CMVi through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- onset of CMV end-organ disease

OR

- initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the participant.

CMV end-organ disease will be determined using the definitions in Appendix 8 and confirmed by an independent CAC. For analysis purposes, the adjudication of cases by the CAC (ie, the final CAC assessment) will take precedence over the investigator's assessment. Only the CAC-confirmed cases of CMV end-organ disease will be included in the CMV end-

organ disease category. However, investigator-assessed CMV end-organ disease cases, which were not confirmed by the CAC but in whom anti-CMV therapy was initiated (in the setting of documented CMV viremia) will be included in the initiation of PET category and, therefore, qualify as having CS-CMVi. Concordance/discordance between CAC and investigator assessment will be summarized.

In this study, any detectable CMV viral DNA result using a local CMV PCR assay is acceptable for documenting viremia as a component of the efficacy endpoint. Documented viremia is defined as any detectable CMV viral DNA obtained immediately prior to (ie, on the day of) the initiation of treatment for CMV disease or PET. In the event that the confirmatory result is not available, a subsequent laboratory result collected from a sample obtained within 7 days will be used. Initiation of anti-CMV therapy without documented CMV viremia will not be considered as a case of CS-CMVi. Similarly, detectable CMV viral DNA alone without initiation of anti-CMV therapy will not be considered as a case of CS-CMVi.

The proportion of participants with CMV disease through Week 14 post-transplant and through Week 24 post-transplant and the proportion of participants with initiation of PET for documented CMV viremia through Week 14 post-transplant and Week 24 post-transplant will also be presented separately.

9.5 Analysis Populations

9.5.1 PK Analysis Population

Per Protocol (PP): The Per-Protocol Population will serve as the primary population for the analyses of PK data in the study. The PP population consists of the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model.

Compliance covers such considerations as exposure to treatment (participants' dosing compliance should be such that their PK is expected to be approaching steady state at the time of intensive PK sampling, availability of measurements and absence of major protocol deviations that may affect the PK assessment. Major protocol deviations will be identified prior to final database lock. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.5.2 Safety Analysis Population

Safety Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all allocated participants who received at least one dose of study intervention. The safety analyses will include all participants who receive any dose of study intervention, but participants who receive different doses in Panels A and B will also be reported separately.

At least one laboratory, vital sign, or ECG measurement obtained after at least one dose of study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 Efficacy Analysis Population

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all allocated participants who receive at least one dose of study intervention and had no detectable CMV viral DNA on Day 1 (when study intervention is initiated). Participants who receive different doses in Panels A and B will also be reported separately.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

9.6.1 Statistical Methods for Pharmacokinetic Analyses

The PK parameters of interest (AUC0-24, Cmax, Ctrough, Ceoi) will be summarized by Age Group and dose level, with geometric means (GMs) and 95% CIs based on natural log-transformed values and the t distribution. Individual AUC0-24, Cmax, Ctrough, and Ceoi values will be plotted by Age Group and dose level as appropriate.

Individual values will also be listed for each PK parameter by Age Group and dose level as appropriate, and the following (nonmodel-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV) (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 × sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log scale). Descriptive statistics will also be provided for concentrations/PK parameters obtained at other time points, as appropriate.

9.6.2 Pharmacokinetic Modeling and Simulation for Dose Selection

Population PK analysis will be performed on all participants who undergo PK sampling, while noncompartmental analysis (NCA) will be performed on the subset of participants who undergo intensive PK in Age Groups 1 and 2 Panel A and Age Group 3.

NCA will be primarily used to verify that the LET exposures in Panel A or Age Group 3 patients are within predetermined bounds believed to be both safe and efficacious based on experience with the Phase 3 adult HSCT population. In the event that any LET exposures in Panel A or Age Group 3 patients are outside the predetermined bounds, an interim population PK analysis will be initiated, based on the Phase 3 population PK model, using all cumulative pediatric PK data, and select PK data from prior Phase 1 and Phase 3 studies. In parallel, the PBPK model will be calibrated to the cumulative pediatric PK data. Both the interim population PK and updated PBPK models will then be used to determine doses for

the Panel B and continuing Age Group 3 participants that are most likely to result in exposures that are within the predetermined bounds.

A final population PK analysis using all cumulative pediatric PK data will be used to establish the PK properties of LET in pediatric patients, enable exposure-efficacy and exposure-safety analyses, and to make final dosing recommendations in the pediatric population for all regimens, age groups, and relevant intrinsic/extrinsic covariates.

An exploratory exposure-response analysis will be conducted relating the HPCD NCA PK parameters to changes in creatinine-based renal function metrics during IV LET administration.

The methodology and employment for both the population PK and NCA methods will be detailed in a separate Modeling & Analysis Plan, and PK-related results reported in a Modeling and Simulation report.

9.6.3 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

The analysis strategy of safety results is summarized in Table 16. The proportions of participants with AEs in the broad categories of any AE, a drug-related AE, a serious AE, an AE, which is both drug-related and serious, and who discontinued study medication due to an AE will be provided along with the corresponding 95% CIs. In addition, deaths will be summarized in the same manner. The 95% CIs for the safety parameters will be estimated using the Clopper-Pearson method [Clopper, C. J. 1934].

The primary safety analysis will summarize the safety data for participants through 28 days following the last dose of study medication. Safety results will be summarized for the APaT population and will also be presented by Age Groups (12 years to <18 years, 2 years to <12 years, birth to <2 years). If doses in Panel A and Panel B are different, results of participants in the Panel B will also be reported separately from those in Panel A. Limited summaries of safety may be provided in participants in Panel A if the starting doses in Panel A and Panel B are different. Adverse events will also be summarized through Week 48 post-transplant.

Table 16 Analysis Strategy for Safety Parameters

Safety Endpoint	Within Group 95% CI	Descriptive Statistics
Any AE	X	X
Any Serious AE	X	X
Any Drug-Related AE	X	X
Any Serious and Drug-Related AE	X	X
Discontinuation due to AE	X	X
Deaths	X	X
Specific AEs, SOCs or PDLCs		X
Change from Baseline results (Labs, ECGs, Vital Signs)		X
AE=adverse event; ECG=electrocardiogram; labs= laboratory values; SOC=System Organ Class; PDLC=Predefined Limit of Change; SOC=System Organ Class; X=results will be provided. 95% CIs will be calculated using the Clopper-Pearson method.		

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format.

Missing safety laboratory, ECGs, or vital signs will be handled using the Data-As-Observed approach, that is, any missing value will be excluded from the analysis. The only exception is when a Baseline/Day 1 result is missing; this will be replaced with the latest pretreatment result, if available.

9.6.4 Statistical Methods for Efficacy Analyses

For the efficacy analysis to estimate the proportion of participants with CS-CMVi through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant, a 95% CI will be calculated based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934]. The same method will be used to analyze all binary endpoints.

The primary efficacy analysis will be performed on the FAS population. A sensitivity analysis including those participants who had detectable CMV viral DNA on Day 1 will be provided. The primary missing data approach will be the Non-Completer= Failure (NC=F) approach (see below for details). Supportive analyses using different missing data approaches will also be conducted (Table 17).

For the analyses of efficacy, results of participants in the Panel B will also be reported separately from those in Panel A, if doses in Panel A and Panel B are different. Limited summaries of efficacy may be provided in participants in Panel A if the starting doses in Panel A and Panel B are different. In addition, key summaries of efficacy will be provided separately by age groups as described in Section 9.10.

Table 17 Analysis Strategy for key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Proportion of participants with clinically significant CMV infection through Week 14 (~100 days) post-transplant	P	95% CI (Clopper-Pearson)	FAS	NC=F
	S	95% CI (Clopper-Pearson)	FAS	OF
	S	95% CI(Clopper-Pearson)	FAS	DAO
Proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant	P	95% CI (Clopper-Pearson)	FAS	NC=F
	S	95% CI (Clopper-Pearson)	FAS	OF
	S	95% CI (Clopper-Pearson)	FAS	DAO

CI=confidence interval; CMV=cytomegalovirus; DAO=Data-as-observed; FAS=full analysis set; NC=F: Non-completer equal failure.(non-completers refer to participants who prematurely discontinued from the study); OF= observed failure; P=primary approach; S=supportive approach.

Missing Data Handling

The primary missing data approach will be the Non-Completer = Failure (NC=F) approach to be consistent with the adult study (P001). Non-completers refer to participants who prematurely discontinued from the study. A participant who had missing efficacy measures at the study time point (eg, Week 24 post-transplant) will be considered as a failure. A participant who discontinued study medication, but remained in the study follow-up will not be considered as a Non-Completer.

Two secondary missing data approaches will be used for supportive analyses. The first is the Observed Failure (OF) approach. Using this approach, participants who were failing (ie, had viremia) when they discontinued prematurely from the study for any reason will be considered as failures, and participants who were not failing (ie, had no viremia) when they discontinued prematurely from the study for any reason will not be considered as failures. The second is the Data-As-Observed (DAO) approach. With this approach, any participant with missing value for a particular endpoint will be excluded from the analysis.

9.6.5 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.5.1 Demographic and Baseline Characteristics

Baseline characteristics for all allocated and treated participants will be summarized by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and allocated, and the

primary reasons for screen failure and discontinuation will be displayed. Demographic variables (eg, age, gender, race), indication for HSCT, prior and concomitant therapies will be summarized for continuous or categorical variables, as appropriate.

9.6.5.2 Palatability and Acceptance Assessment

Each participant will rate the palatability and respond to questions on the acceptability of treatment with oral granules on the first day of oral granule administration and one week later. This will be based on the FHS facial expression scale depicting various degrees of pleasure as an assessment of palatability (Section 4.2.1.4 and Section 8.10).

Descriptive statistics will be used to summarize the palatability and acceptability responses. Missing data will not be imputed, and the analyses will be based on observed data only. These analyses will be based on the APaT population.

9.7 Interim Analyses

Initial PK evaluations will be conducted as described in Section 4.3.1.

To supplement the routine safety monitoring outlined in this protocol, an external DMC will be appointed to monitor ongoing safety data and provide recommendations to discontinuation of the study or protocol modifications to the EOC (see Appendix 1 Committees Structure–Executive Oversight Committee). The DMC will periodically review the safety data at the following proposed time points:

1) when 6 PK-evaluable participants in Age Group 1, Panel A have completed intensive PK sampling at the Day 7 visit

2) when 6 PK-evaluable participants in Age Group 2, Panel A have completed intensive PK sampling at the Day 7 visit

3) when ~10 (which is ~50%) of participants in Age Group 1, Panel B have completed the Week 4 visit

4) when ~10 (which is ~50%) of participants in Age Group 2, Panel B have completed the Week 4 visit

5) when at least 3 participants in Age Group 3 have completed intensive PK sampling

Some DMC reviews may be combined at the request of the DMC. The DMC may review safety data at other time points (including after the last scheduled safety check) as needed. DMC reviews are primarily based on safety, but any available efficacy data will be provided upon request to facilitate a benefit-risk evaluation.

Study enrollment for an age group will be paused until after the interim PK analyses, and reevaluation of the initial dose for the age group at the indicated time points, as shown in Figure 2 are completed independent of DMC review of safety data. An internal statistician

not otherwise connected with the study will conduct analyses and present results to the DMC. Additional logistical details will be provided in the DMC Charter.

9.8 Multiplicity

There will be no multiplicity adjustments in the analysis of this study.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for PK Analysis

A sample size of 6 in Age Group 1 and 2 has approximately 95% power to show that the 95% confidence interval of the geometric mean of AUC0-24 in this age group will be within 60% and 140% of the geometric mean estimates of the AUC0-24 of LET. A between-subject standard deviation of 0.325 in log scale for AUC0-24 that was obtained from previous studies (P003 and P004) was used for these calculations. This calculation is based on the pediatric guidance proposed by Wang et al [Wang, Y., et al 2012].

A sample size of 8 in Age Group 3 has approximately 99% power to show that the 95% confidence interval of the geometric mean of AUC0-24 in this age group will be within 60% and 140% of the geometric mean estimates of the AUC0-24 of LET. A between-subject standard deviation of 0.325 in log scale for AUC0-24 that was obtained from previous studies (P003 and P004) was used for these calculations. This calculation is based on the pediatric guidance proposed by Wang et al [Wang, Y., et al 2012].

9.9.2 Sample Size and Power for Safety Analysis

This study will allocate 60 participants to receive LET. A total of at least 26 participants will be enrolled for each of the 2 oldest age groups. As this will be a descriptive study, the sample size used in this study is not based on statistical considerations.

The probability of observing at least one of a particular AE in this study depends on the number of participants treated and the underlying percentage of participants with that AE in the study population. If the underlying incidence of a particular AE is 1% (1 of every 100 participants receiving the drug), there is a 45% chance of observing at least one of that particular AE among 60 participants. For analyses by Age Group, there is a 23% chance of observing at least one of that particular AE among 26 participants or an 8% chance of observing at least one of that particular AE among 8 participants. If no AE of that particular type are observed among the 26 participants, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <13.2% (one in every 8 participants). If no AE of that particular type are observed among the 8 participants, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <36.9% (one in every 3 participants).

The estimate of and the upper bound of the 95% confidence interval for the underlying percentage of participants with a particular AE given various hypothetical observed number

of participants with the AE are provided in Table 18. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934].

Table 18 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants With AEs

	Hypothetical Number of Participants with an AE (Estimate of Incidence, %)	95% Upper Confidence Bound[a]
N=8	0 (0)	36.9
	1 (12.5)	52.7
	2 (25.0)	65.1
N=26	0 (0)	13.2
	1 (3.8)	19.6
	2 (7.7)	25.1
N=60	0 (0)	6.0
	1 (1.7)	8.9
	2 (3.3)	11.5
	5 (8.3)	18.4

AE(s)=adverse event(s); N=number of participants.
[a] Based on the two-sided exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).

9.9.3 Sample Size and Power for Efficacy Analysis

This is a descriptive study with no hypotheses. A total of at least 26 participants will be enrolled for each of the 2 oldest age groups. The key efficacy objective will be assessed based on the proportion of participants with CS-CMVi through Week 24 (~6 months) post-transplant. The expected rate of participants with CS-CMVi through Week 24 post-transplant is ~18% based on P001 data and assuming LET is expected to be similarly active in adults and pediatric participants. Since the primary missing data approach will be NC=F approach, 25% was added to the expected incidence of CS-CMVi through Week 24 post-transplant with the assumption that higher discontinuation rate will be observed in the more vulnerable pediatric participants than adults. In terms of estimation with the proposed sample size, with 26 participants, the maximum half-width of the 95% exact confidence interval will be no greater than 21%. The calculation is based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934] and is carried out using SAS v9.4. Table 19 shows the 95% CIs for CS-CMVi given varying assumptions of number of failures for 8, 26, and 60 participants. Note that the intervals are not symmetric around the point estimate.

Table 19 Two-sided 95% Confidence Intervals for the Proportion of Participants With Clinically Significant CMV Infection Through Week 24 (~6 Months) Post-transplant (FAS Population)

	Number of Failures[a] (%)	Two-Sided 95% Confidence Interval[b]
N=8	2 (25.0)	(3.2, 65.1)
	3 (37.5)	(8.5, 75.5)
	4 (50.0)	(15.7, 84.3)
N=26	9 (34.6)	(17.2, 55.7)
	10 (38.5)	(20.2, 59.4)
	11 (42.3)	(23.4, 63.1)
	12 (46.2)	(26.6, 66.6)
N=60	19 (31.7)	(20.3, 45.0)
	21 (35.0)	(23.1, 48.4)
	23 (38.3)	(26.1, 51.8)
	25 (41.7)	(29.1, 55.1)
	27 (45.0)	(32.1, 58.4)

CMV=-cytomegalovirus; FAS=full analysis set; N=number of participants.
[a] Based on Non-Completer = Failure approach.
[b] Based on the two-sided exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).

9.10 Subgroup Analyses

To assess the consistency of the response across various subgroups, the proportion of participants with CS-CMVi through Week 14 (~100 days) post-transplant and associated 95% CIs will be estimated within each category of the following classification variables:

- Age category (birth to <2 years, 2 years to <12 years, 12 years to <18 years)
- Sex (female, male)
- Race (white, black, Asian, other)
- Donor and/or Recipient Serostatus

The consistency of the response will be assessed descriptively via summary statistics by category for the classification variables listed above. Other clinically relevant variables may be identified for which additional subgroup analyses may be performed.

9.11 Compliance (Medication Adherence)

Drug accountability data for LET will be collected during the study. A day within the study will be considered an "On-Therapy" day if the participant takes at least one dose. For a participant who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from treatment allocation to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from treatment allocation to the date of the last dose of study intervention.

For each participant, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100$$

Summary statistics will be provided on percent compliance for the APaT population.

In addition, percent of participants on CsA and duration of CsA use will be reported.

9.12 Extent of Exposure

The extent of exposure to study intervention will be evaluated by summary statistics (N, mean, and range) for the "Number of Days on Therapy".

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutiona Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Clinical Adjudication Committee (CAC)

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Appendix 8, as well as evaluating the presence of confounding factors.

The CAC will review clinical, virological, and histopathological data as well as the investigator's assessment for adjudicating all potential cases of CMV end-organ disease. CMV end-organ disease will be determined using the definitions in Appendix 8.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their

disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants, documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests specified in Table 20 will be performed by the site's **local** laboratory. The tests specified in Table 21 will be performed by the **central** laboratory. Local laboratory results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 20 Protocol-required Laboratory Assessments (Local Laboratory)

Laboratory Assessments	Parameters			
Hematology	Platelet Count	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
	Hemoglobin			
	Hematocrit			
Chemistry	Blood Urea Nitrogen (BUN) If BUN testing is not available at the local laboratory, blood urea must be measured and reported.	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin and direct bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Urine or serum β human chorionic gonadotropin (β hCG) pregnancy test (for WOCBP). • Serology: (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus (HCV) antibody (screening only). • HCV RNA PCR: to be done only in participants who test positive for HCV antibody (screening only) • Coagulation: PT/INR • Creatinine Clearance; calculated using the Cockcroft-Gault equation for participants ≥12 years of age or the modified Schwartz equation for participants <12 years of age (Appendix 12) • CMV DNA PCR using plasma or whole blood • pp65 antigen test (to be **only** reported by sites in Japan using the test **in addition** to CMV DNA PCR test results)			

Table 21 Protocol-required Laboratory Assessments (Central Laboratory)

Laboratory Assessments/Parameters
Plasma sample for cytomegalovirus (CMV) DNA Sequence Analysis: CMV DNA Sequence Analysis to be performed only in participants with clinically significant cytomegalovirus infection (CS-CMVi)and who have detectable CMV DNA.
PK samples testing Planned genetic analysis specimen (buccal swab) Future Biomedical Research will be conducted on residual DNA collected from buccal swab as well as leftover main study plasma from CMV viral resistance

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Table 22, Table 23, and Table 24 summarize the approximate blood volumes collected by study visit and sample types for the research testing (central labs), in separate tables by Age Group.

Table 22 Approximate Blood Volumes Drawn/Collected by Study Visit and by Sample Types – Research Testing (Age Group 1)

		Treatment Period															Follow-up Period							
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	25	26	**Expected Maximum Total Blood Volume per participant**
Visit Name	SCR	D1	D7	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W16	W18	W20	W22	W24	CMV Infection Visit	Early Study Discon Visit	
Research Testing (Central Labs)																								
CMV DNA Sequence Analysis																						3 [a]		**3**
Sparse PK				3		3		3		3		3		3		3						3[b]	3[c]	**21**
Intensive PK [c]			15																					**15**
Expected Total (mL)	**0**	**0**	**15**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**0**	**0**	**0**	**0**	**6**	**3**	**39**

CMV=cytomegalovirus; CS-CMVi=clinically significant cytomegalovirus infection; Discon=discontinuation; PK=pharmacokinetics.
Note: This table is based on the estimated maximum volume (in mL) to be required for each test.
[a] Performed only in participants with CS-CMVi. **Plasma** samples required.
[b] Done only if the visit occurs during the Treatment Period. No subsequent Sparse PK samples would be taken.
[c] Refer to Section 8.6 for details.

Table 23 Approximate Blood Volumes Drawn/Collected by Study Visit and by Sample Types – Research Testing (Age Group 2)

		Treatment Period															Follow-up Period							
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	25	26	**Expected Maximum Total Blood Volume per participant**
Visit Name	SCR	D1	D7	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W16	W18	W20	W22	W24	CMV Infection Visit	Early Study Discon Visit	
Research Testing (Central Labs)																								
CMV DNA Sequence Analysis																						2 [a]		**2**
Sparse PK				1		1		1		1		1		1		1						1 [b]	1 [b]	**7**
Intensive PK [c]			5																					**5**
Expected Total (mL)	**0**	**0**	**5**	**1**	**0**	**1**	**0**	**1**	**0**	**1**	**0**	**1**	**0**	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**3**	**1**	**14**

CMV=cytomegalovirus; CS-CMVi=clinically significant cytomegalovirus infection; PK=pharmacokinetics.
Note: This table is based on the estimated maximum volume (in mL) to be required for each test.
[a] Performed only in participants with CS-CMVi. **Plasma** samples required.
[b] Done only if the visit occurs during the Treatment Period. No subsequent Sparse PK samples would be taken.
[c] Refer to Section 8.6 for details.

Table 24 Approximate Blood Volumes Drawn/Collected by Study Visit and by Sample Types – Research Testing (Age Group 3)

	Treatment Period																Follow-up Period							
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	25	26	**Expected Maximum Total Blood Volume per participant**
Visit Name	SCR	D1	D7	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W16	W18	W20	W22	W24	CMV Infection Visit	Early Study Discon Visit	
Research Testing (Central Labs)																								
CMV DNA Sequence Analysis																						1 [a]		**1**
Sparse PK				0.25		0.25		0.25		0.25		0.25		0.25		0.25						0.25[b]	0.25[b]	**2.25**
Intensive PK [c]			1.25																					**1.25**
HPCD PK sampling[d]			0.5																					**0.5**
Expected Total (mL)	**0**	**0**	**1.75**	**0.25**		**0.25**		**0.25**		**0.25**		**0.25**		**0.25**		**0.25**						**1.25**	**0.25**	**5.0**

CMV=cytomegalovirus; CS-CMVi=clinically significant cytomegalovirus infection; Discon=discontinuation; HPCD=hydroxypropyl-beta-cyclodextrin; LET=letermovir; PK=pharmacokinetics.
Note: This table is based on the estimated maximum volume (in mL) to be required for each test.
[a] Performed only in participants with CS-CMVi.
[b] Done only if the visit occurs during the Treatment Period. No subsequent Sparse PK samples would be taken.
[c] Refer to Section 8.6 for details. Collection will start on the 5th consecutive day of IV dosing.
[d] Start on the 4th consecutive day of IV dosing. See Sections 8.6.2 and 8.6.2.1 for additional sampling for serum creatinine with HPCD PK sampling.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

    - The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?

- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the study intervention in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study intervention(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).

  - Yes, there is a reasonable possibility of study intervention relationship:

    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

  - No, there is not a reasonable possibility of study intervention relationship:

    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not Applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

- Premenarchal

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.5.2 Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to start contraception when initiating sexual activity and they agree to use one of the contraception methods described in Table 25 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 25 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). b If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those, which inhibit ovulation.

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of study intervention, additional pregnancy testing will be performed at monthly intervals during the treatment period and until approximately 28 days following the last dose of study medication per the SoA.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research [3,4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3,4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3,4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3,4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3,4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3,4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3,4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3,4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3,4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3,4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@msd.com.

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10.7 Appendix 7: Country-specific Requirements

Not Applicable.

10.8 Appendix 8 Definition of CMV Disease in Hematopoietic Stem Cell Transplant (HSCT) Recipients

CMV Disease Type	Probable	Proven	Notes
Pneumonia	Signs and/or symptoms of pneumonia **AND** Detection of CMV by viral isolation, rapid culture of BAL fluid, or the quantitation of CMV DNA in BAL fluid	Signs and/or symptoms of pulmonary disease **AND** Detection of CMV in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques	• PCR may be too sensitive, so detection of CMV by PCR alone is insufficient for the diagnosis of CMV pneumonia. • Superinfection or coinfection with other pathogens may occur and should be noted when present.
GI Disease	Symptoms of upper and/or lower GI disease **AND** Evidence of CMV in tissue but without the requirement for macroscopic mucosal lesions	Symptoms of upper and/or lower GI disease **AND** Macroscopic mucosal lesions **AND** Detection of CMV in GI tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization	• Detection of CMV by PCR alone is insufficient for the diagnosis of CMV GI disease.
Hepatitis	N/A	Abnormal liver function tests **AND** CMV documented in tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques **AND** Absence of other documented cause of hepatitis	• Detection of CMV by PCR alone is insufficient as it may represent transient DNAemia. Hence, PCR is insufficient to diagnose CMV hepatitis. • Documentation of CMV in liver biopsy specimen (ie, by culture, histopathology, immunohistochemical analysis or in situ hybridization) is needed. • Coinfection with other pathogens like HCV may be present without excluding the diagnosis of CMV hepatitis.

CMV Disease Type	Probable	Proven	Notes
Encephalitis / ventriculitis	CNS symptoms **AND** Abnormal imaging results or evidence of encephalitis on electroencephalography **AND** Detection of CMV in CSF without visible contamination of blood	CNS symptoms **AND** Detection of CMV in CNS tissue by virus isolation, rapid culture, immunohistochemistry, in situ hybridization, or (preferably) quantitative PCR	N/A
Retinitis	N/A	Lesions typical of CMV retinitis confirmed by an ophthalmologist.	N/A
Nephritis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or in situ hybridization in a kidney biopsy specimen obtained from a patient with renal dysfunction AND Identification of histologic features of CMV infection	• Detection of CMV in urine by PCR or culture is insufficient for the diagnosis of CMV nephritis.
Cystitis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or in situ hybridization in a bladder biopsy specimen obtained from a patient with cystitis AND Identification of conventional histologic features of CMV infection	• Detection of CMV in urine by PCR or culture is insufficient for the diagnosis of CMV cystitis.
Myocarditis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or in situ hybridization in a heart biopsy specimen obtained from a patient with myocarditis AND Identification of conventional histologic features of CMV infection	N/A

CMV Disease Type	Probable	Proven	Notes
Pancreatitis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or in situ hybridization in a pancreatic biopsy specimen obtained from a patient with pancreatitis AND Identification of conventional histologic features of CMV infection	N/A
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BAL=bronchoalveolar lavage; CMV=cytomegalovirus; CNS=central nervous system; CSF=cerebrospinal fluid; DNA=deoxyribonucleic acid; GI=gastrointestinal; HCV=hepatitis C virus; PCR=polymerase chain reaction; ULN=upper limit of normal.			

[Ljungman, P., et al 2016] [National Cancer Institute 2009]

10.9 Appendix 9 Child-Pugh Classification for Severity of Liver Disease

	Scoring by Anomaly		
Signs or symptom	**1 point**	**2 points**	**3 points**
Hepatic encephalopathy[a]	absent	Grade 1 or Grade 2	Grade 3 or Grade 4
Ascites	absent	mild	moderate /severe
Bilirubin (mg/dL)	<2 mg/dL	2 – 3 mg/dL	>3 mg/dL
Albumin (g/dL)	>3.5 g/dL	2.8 – 3.5 g/dL	<2.8 g/dL
INR	<1.7	1.7 – 2.3	>2.3

INR=international normalized ratio
[a]Hepatic encephalopathy grading:
Grade 1: Altered mood/confusion
Grade 2: Inappropriate behavior, impending stupor, somnolence
Grade 3: Markedly confused, stuporous but arousable
Grade 4: Comatose/unresponsive

Child-Pugh Score Interpretation	
5 – 6 points	Child-Pugh Stage A (mild hepatic insufficiency)
7 – 9 points	Child-Pugh Stage B (moderate hepatic insufficiency*)
>10 points	Child-Pugh Stage C (severe hepatic insufficiency)

*If hypoalbuminemia is the only abnormality noted, the participant will need to have a score of ≥7 to qualify for moderate hepatic insufficiency for this study.

10.10 Appendix 10: Medications Allowed for HSV/VZV Prophylaxis

10.10.1 Acyclovir

10.10.1.1 HSV Prophylaxis

Prevention of early reactivation

Note: Begin at conditioning and continue until engraftment or resolution of mucositis; whichever is longer (~30 days post-HSCT).

Infants, Children, and Adolescents <40 kg:

IV: 250 mg/m^2/dose every 8 hours or 125 mg/m^2/dose every 6 hours; maximum daily dose: 80 mg/kg/day

Oral: 60 to 90 mg/kg/day in 2 to 3 divided doses; maximum dose: 800 mg/dose twice daily

Children and Adolescents ≥40 kg:

IV: 250 mg/m2/dose every 12 hours

Oral: 400 to 800 mg twice daily

Prevention of late reactivation

Note: Treatment during first year after HSCT.

Infants, Children, and Adolescents <40 kg:

Oral: 60 to 90 mg/kg/day in 2 to 3 divided doses; maximum daily dose: 800 mg twice daily

Children and Adolescents ≥40 kg:

Oral: 800 mg twice daily

10.10.1.2 Varicella (Chickenpox) or Herpes Zoster (Shingles), Prophylaxis

Hematopoietic stem cell transplant (HSCT): Prophylaxis of disease reactivation

Note: Continue therapy for 1 year after HSCT [Tomblyn, M, et al 2009].

Infants, Children, and Adolescents <40 kg:

Oral: 60 to 80 mg/kg/day in 2 to 3 divided doses

Children and Adolescents ≥40 kg:

Oral: 800 mg twice daily

10.10.2 Valacyclovir

10.10.2.1 Herpes Simplex Virus (HSV), Prophylaxis

Immunocompromised patients (eg, HSCT or leukopenic oncology patients)

Limited data available ([Tomblyn, M, et al 2009])

Children and adolescents, oral:

Early reactivation prevention

Begin at initiation of conditioning and continue until engraftment or resolution of mucositis (IDSA [Tomblyn, M, et al 2009])

Patient weight <40 kg:

250 mg twice daily

Patient weight ≥40 kg:

500 mg once or twice daily; twice daily dosing should be considered in patients who are highly suppressed

Late reactivation prevention

Continue throughout the first year following HSCT ([Tomblyn, M, et al 2009])

Patient weight <40 kg:

250 mg twice daily

Patient weight ≥40 kg:

500 mg once or twice daily; twice daily dosing should be considered in patients who are highly suppressed

10.10.2.2 Varicella (Chickenpox), Prophylaxis

Immunocompromised patients (eg, HSCT or leukopenic oncology)

Limited data available

Children and adolescents:

Weight-directed:
Oral: 15 to 30 mg/kg/dose 3 times daily ([Bomgaars, L., et al 2008])

Fixed dosing:

Patient weight <40 kg:

Oral: 250 or 500 mg twice daily ([Tomblyn, M, et al 2009])

Patient weight ≥40 kg:

Oral: 500 mg twice daily ([Tomblyn, M, et al 2009])

Post exposure prophylaxis (IDSA [Tomblyn, M, et al 2009]):

Note: Continue for 22 days post exposure.

Patient weight <40 kg:

Oral: 500 mg 3 times daily

Patient weight ≥40 kg:

Oral: 1,000 mg 3 times daily

10.11 Appendix 11: Palatability and Acceptance Assessment Form

LET FOR THE PREVENTION OF CMV INFECTION/DISEASE IN PEDIATRIC HSCT RECIPIENTS

PAA

Compound	Protocol	Visit	Screening No. (Site - Sequence No.)	Randomization No.
MK-8228	030		_ _ _ _ - _ _ _ _ _	_ _ _ _ _ _ _

PALATABILITY AND ACCEPTANCE ASSESSMENT (PAA)

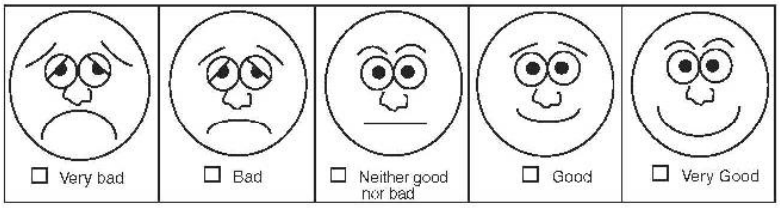
Specify completion date: DD-MM-YYYY

Please mark one box below to identify the person entering the responses on the questionnaire.

- ☐ The patient
- ☐ The parent/primary caregiver
- ☐ The patient and parent/primary caregiver
- ☐ The health care provider (e.g., physician, nurse, medical assistant or nursing assistant caring for the patient)

This form should be completed at the time of oral medication administration.
Please answer all questions.

1. Please mark the box of one picture below to show how you/the patient feels about the taste of the medication:



☐ Very bad ☐ Bad ☐ Neither good nor bad ☐ Good ☐ Very Good

2. Please indicate if you/the patient had any of the following problems when taking the medication by mouth:

a. Refusing	☐ Yes	☐ No
b. Spitting Out	☐ Yes	☐ No
c. Throwing Up or Spitting Up	☐ Yes	☐ No
d. Gagging	☐ Yes	☐ No
e. Other, specify	☐ Yes	☐ No _____

3. Are there any other comments related to the taste of the medication? ☐ Yes ☐ No

Specify comments: _____

_____

_____

I confirm this information is accurate.	Subject's/Caregiver's Initials:	Date:

I have reviewed this information.	Staff Initials:	Date:

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10.12 Appendix 12: Calculation of Creatinine Clearance by Age of Study Participant

Food and Drug Administration guidance recommends using Cockcroft-Gault equation in adolescents ≥12 years of age and the modified Schwartz equation for infants and children <12 years of age [Food and Drug Administration (CDER) 2014].

Cockcroft-Gault Equation (for Participants ≥12 Years of age):

$$\text{Creatinine clearance (males)} = \frac{(\text{weight in kg}) \times (140 \text{ minus age})}{(72) \times (\text{creatinine in mg/dL})}$$

Creatinine clearance (females) = 0.85 × the value obtained using the equation above

Modified Schwartz Equation (for Participants <12 Years of age):

$$\text{Creatinine clearance} = \frac{K \times (\text{height in cm})}{(\text{creatinine in mg/dL})}$$

K (proportionality constant):
Infant (term <1 year): K=0.45
Female child (≥1 year and <12 years): K=0.55
Male child (≥1 year and <12 years): K=0.70

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	All Participants as Treated
AST	aspartate aminotransferase
AUC0-24	area under the concentration-time curve for the dosing period (0 to 24 hours)
AUC0-inf	area under the concentration-time curve for the dosing period (0 to infinity)
CAC	Clinical Adjudication Committee
Ceoi	concentration at the end of infusion
CI	confidence interval
CL	clearance
CL/F	apparent clearance
Cmax	maximum concentration observed
CMV	Cytomegalovirus
CMVi	Cytomegalovirus infection
CNS	central nervous system
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CrCl	creatinine clearance
CRF	Case Report Form
CsA	Cyclosporin A
CS-CMVi	Clinically significant CMV infection
CSR	clinical study report
Ctrough	minimum concentration observed before next dose
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DEHP	diethylhexyl phthalate
DILI	drug-induced liver injury
Discon	Discontinuation
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DAO	data-as-observed
EBMT	European Group for Blood and Marrow Transplantation
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FHS	facial hedonic scale
FSH	Follicle stimulating hormone
G tube	Gastric tube
GCP	Good Clinical Practice
GM	geometric mean
GMR	geometric mean ratios

Abbreviation	Expanded Term
GVHD	graft-versus-host disease
HBsAG	hepatitis B surface antigen
HCV	hepatitis C virus
HCV-Ab	hepatitis C virus antibody
HHV	human herpes virus
HIV	human immunodeficiency virus
HIV-Ab	human immunodeficiency virus antibody
HPCD	hydroxypropyl-beta-cyclodextrin
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
IA(s)	Interim Analysis (ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LET	Letermovir
NC=F	Non-Completer=Failure
NCA	Noncompartmental analysis
NG tube	Nasogastric tube
NTR	narrow therapeutic range
OF	observed failure
PAA	Palatability Acceptance Assessment
PCL	Protocol Clarification Letter
PCR	polymerase chain reaction
PES	polyethersulfone
PET	preemptive therapy
PBPK	physiologically based pharmacokinetics
PK	pharmacokinetics
PP	Per Protocol
PT	prothrombin time
QD	once daily
QP2	department of quantitative pharmacology and pharmacometrics
R+	CMV-seropositive recipients
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
siDMC	Standing Internal Data Monitoring Committee
SMD	study medication diary
SoA	schedule of activities
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
t1/2	half-life

Abbreviation	Expanded Term
Tmax	time to maximum concentration observed
ULN	upper limit of normal
Vd	volume of distribution
VZV	varicella zoster virus
WOCBP	woman/women of childbearing potential

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